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Sulfonylammonium Ions: Applications In Mechanistic And Synthetic Organosulfur Chemistry

John David Lock

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SULFONYLAMMONIUM IONS: APPLICATIONS IN MECHANISTIC AND SYNTHETIC ORGANOSULFUR CHEMISTRY

By

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Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

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The University of Western Ontario
London, Ontario

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ABSTRACT

This thesis describes the results obtained from two projects in organosulfur chemistry, both of which involve the use of sulfonylammonium ions. The two projects undertaken involved sulfenes and 3-alkoxysulfonyl trialkylpropanaminium salts ("[3]betylates").

The first project describes efforts undertaken to delineate more precisely the reaction mechanisms of sulfenes, a highly reactive species. The reaction mechanism of sulfene was studied by allowing multiexchange to occur with deuterated traps. Methanol-d was used as the trapping agent in benzene-acetonitrile and deuterium oxide as the trap in a buffered deuterium oxide-dimethoxyethane system. The investigations made use of methanesulfonyl chloride and a series of trialkyl(methylsulfonyl)ammonium fluorosulfate salts as starting materials. The multiexchange results were used to deduce aspects of the mechanism. The results obtained showed that nucleophilic catalysis was not a significant path for formation of sulfene from sulfonyl chlorides when triethylamine was used to promote sulfene formation but that less hindered amines may react with methanesulfonyl chloride via nucleophilic catalysis to some extent.

The second project involves the synthesis and reactions of [3]Betylates (3-(alkoxysulfonyl)propanaminium salts). [3]Betylates are an example of a new type of substrate for aliphatic nucleophilic substitution which enhance the applicability of nucleophilic substitution reactions to problems in organic synthesis by providing a good nucleofuge and phase transfer reagent in one substrate. Unlike

their lower homologs, the 2-(alkoxysulfonyl)-ethanaminium salts ([2]betylates), the [3]betylates were found to be quite stable to elimination and thus allow clean nucleophilic substitution with a wider variety of nucleophiles. Although [3]betylates are somewhat less reactive than [2]betylates they appear to be able to undergo any reaction characteristic of a [2]betylate. The [3]betylates were synthesized by the reaction of a cyclic sulfonylammonium ion (2,2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate) with alcohols and triethylamine.

to my parents and AEH

ACKNOWLEDGEMENTS

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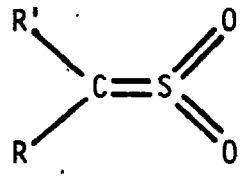
CHAPTER 1

THE MULTIEXCHANGE REACTIONS OF THE METHYLSULFONYLAMMONIUM SALTS AND METHANESULFONYL CHLORIDE IN DEUTERIUM OXIDE-DIMETHOXYETHANE

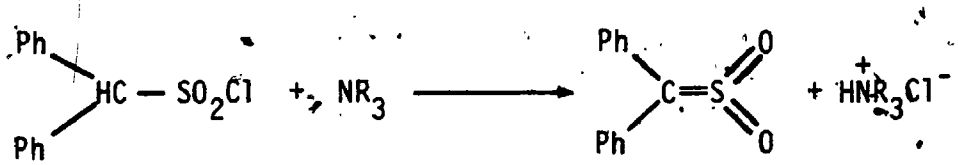
1.1 Introduction

In 1911 Wedekind and Schenk (1) proposed the term "sulfene" for the species shown below where R = R' = H. The authors also undertook the first attempt to synthesize an example of this class of compound as



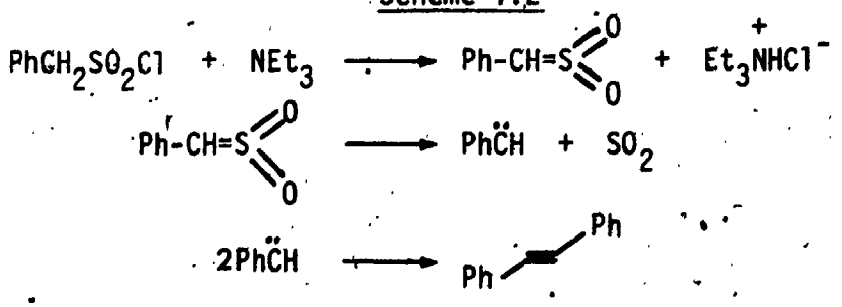
previous work on the carbon analog of sulfenes, ketenes, led the authors to believe that diphenylsulfene could be isolated from the reaction of diphenylmethanesulfonyl chloride with base (see Scheme 1.1). Unfortunately, Wedekind and Schenk could not obtain diphenylmethanesulfonyl

Scheme 1.1



chloride. Therefore the reaction was attempted with phenylmethanesulfonyl chloride and triethylamine. This did not result in the isolation of phenylsulfene but gave trans-stilbene and triethylammonium chloride. The mechanism suggested by these authors is shown in Scheme 1.2. More recent work has shown that the first step of this scheme is probably

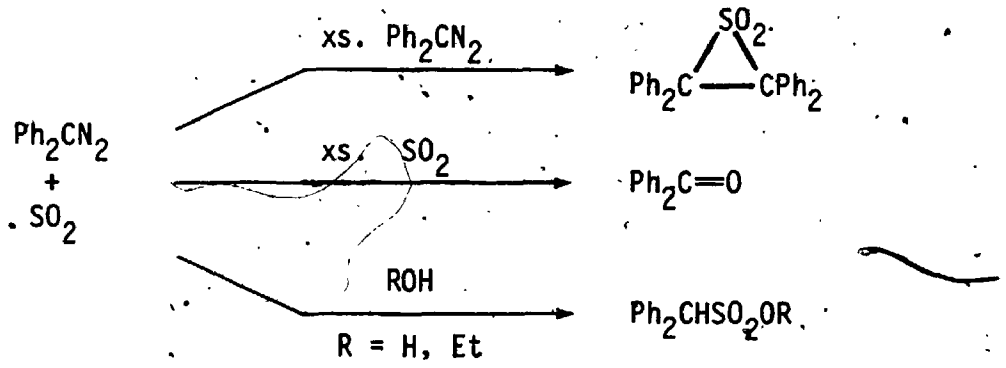
Scheme 1.2



correct, the details of which have been well summarized (2,3).

Later, in 1916, Staudinger and Pfenninger (4), investigated the reaction of diphenyldiazomethane with sulfur dioxide as a source of the sulfene. Their observations are summarized in Scheme 1.3. The authors proposed that the reaction proceeded via diphenylsulfene formation although the formation of acid and ester could be explained without invoking sulfene.

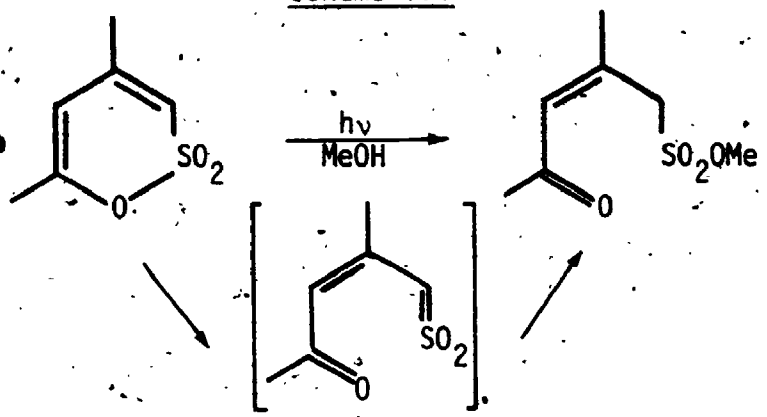
Scheme 1.3



After this initial work there was little discussion of sulfenes and their chemistry until 1952 when Backer and Kloosterziel published the first of a series of papers (5-7) which extended and clarified the experiments of Staudinger and Pfenninger. In 1957 Hesse and coworkers (8-10) extended this work further making a reference to sulfenes.

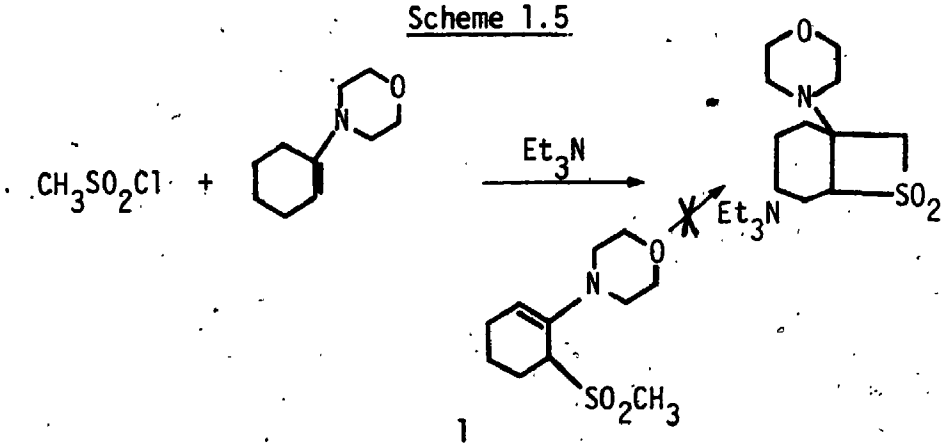
In the early 1960's a number of groups reported some completely new sulfene chemistry. In 1961, Henmo et al.(11) reported that irradiation of six-membered ring dienic sultones with ultraviolet light gave products compatible with those expected from a sulfene produced from photochemical cycloreversion of a cyclohexadiene systems (see Scheme 1.4).

Scheme 1.4



In 1962, two papers, by Stork and Borowitz (12) and Opitz and Fischer (13), reported that the reaction of an enamine with methanesulfonyl chloride in the presence of triethylamine gave a sulfene-enamine adduct as illustrated in Scheme 1.5. The inability of 1 to

Scheme 1.5



1

form the enamine-sulfene adduct (14,15) was taken as good evidence for the presence of sulfene, since the reaction of 1 to form the adduct had been the most likely alternative to a sulfene reaction.

Another test for sulfene was performed shortly afterwards by King and Durst (16,17) and Truce and coworkers (18,19). This test was based on the idea that a sulfene would react with an appropriately deuterated trap (e.g. D_2O) to give a product with one atom of deuterium per molecule

as outlined in Scheme 1.6. Direct substitution to displace the leaving group attached to the sulfonyl group would give undeuterated product. Any process which would give a random exchange - such as formation of a carbanion from methanesulfonyl chloride - would be detectable as a

Scheme 1.6

$$CH_3SO_2Cl + Et_3N \longrightarrow CH_2{=}SO_2 + Et_3\overset{+}{N}HCl^-$$

$$CH_2 = SO_2 + DZ \longrightarrow CH_2D - SO_2Z$$

mixture of non, mono, di and trideuterated products. The results obtained by King and Durst are summarized in Table 1.1. Since the products obtained were those in which one and only one alpha hydrogen was exchanged this was strong evidence for the intermediacy of a sulfene and the exclusion of nonsulfene reactions.

The results reported by Truce and coworkers were qualitatively similar to those of King and Durst. The triethylamine catalyzed reaction of methanesulfonyl chloride with methanol-d in benzene gave a mixture of non and monodeuterated methyl mesylate (see Table 1.2). No sign of di- or trideuterated ester was found by nmr or mass spectrometry. Since a large amount of the product did not show the incorporation of an atom of deuterium the authors proposed that the reaction was taking place by two competing pathways, an S_N2 pathway to form the methylsulfonylammonium salt 2 and an E2 elimination to form sulfene (see Scheme 1.7). Product formation was then proposed to occur via nucleophilic substitution on 2 or by sulfene trapping. The observed increase in monodeuteration with more trap was rationalized in terms of a competition between sulfene trapping and "collapse" of the sulfene with triethylamine

Table 1.1. Deuterium Incorporation Results in the Triethylamine Induced Solvolysis of Alkanesulfonyl Chlorides[a].

Substrate (mmol)	Trap (mmol)	Monodeuteration in Percent
$PhCH_2SO_2Cl$ (11)	D_2O (22)	97.5
$PhCH_2SO_2Cl$ (1.9)	2-propanol-$\underline{d}$[b] (excess)	91
CH_3SO_2Cl (39)	D_2O (900)	72
$CH_3CH_2SO_2Cl$ (35)	D_2O (900)	93

a: from King and Durst (17)

b: the alcohol was estimated to be 92 ± 2% active deuterium.

Table 1.2. Percent Monodeuteration Obtained by Reaction of Methanesulfonyl Chloride with Methanol-d using Triethylamine as Catalyst[a,b]

MeOD (mmol)	solvent	Monodeuteration[c] %
120	benzene	47.7
400	benzene	81.4
120	hexane	45[d]

a: 100 mmol of the sulfonyl chloride and 130 mmol of the base were used.

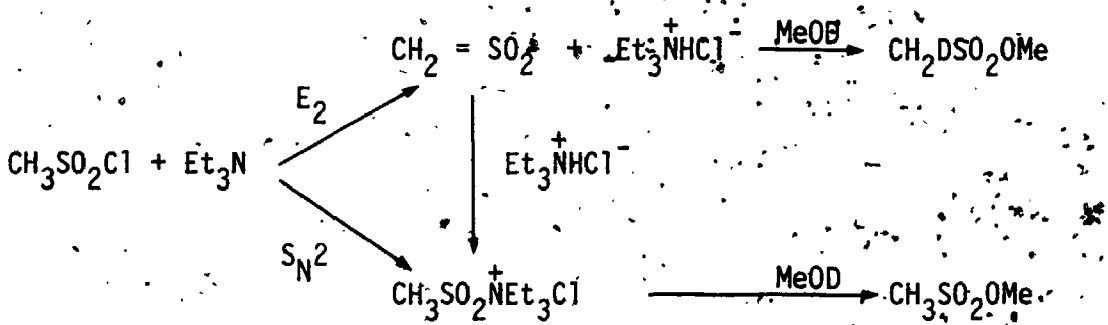
b: from Truce and Campbell (19).

c: no sign of di or trideuteration was found. The remainder of the product (methyl mesylate) was nondeuterated.

d: estimated value.

hydrochloride, the former being relatively favored by the increase in methanol-d concentration. The reaction pathways shown in Scheme 1.7 will be discussed further in chapter 2 in the context of the possibility that the protium abstracted from the sulfonyl chloride during sulfene formation reappears in the product ester. The extent of any possible contribution of nucleophilic catalysis to this reaction will also be considered.

Scheme 1.7



2

In 1969 King and Lee (20) examined the kinetics of the reaction of methanesulfonyl chloride with triethylamine and a variety of traps at -25°C in 1,2-dimethoxyethane. The rate of the reaction could be measured by isolation of N-phenylmethanesulfonamide or by titration of the chloride produced. The results were consistent with the following rate expression:

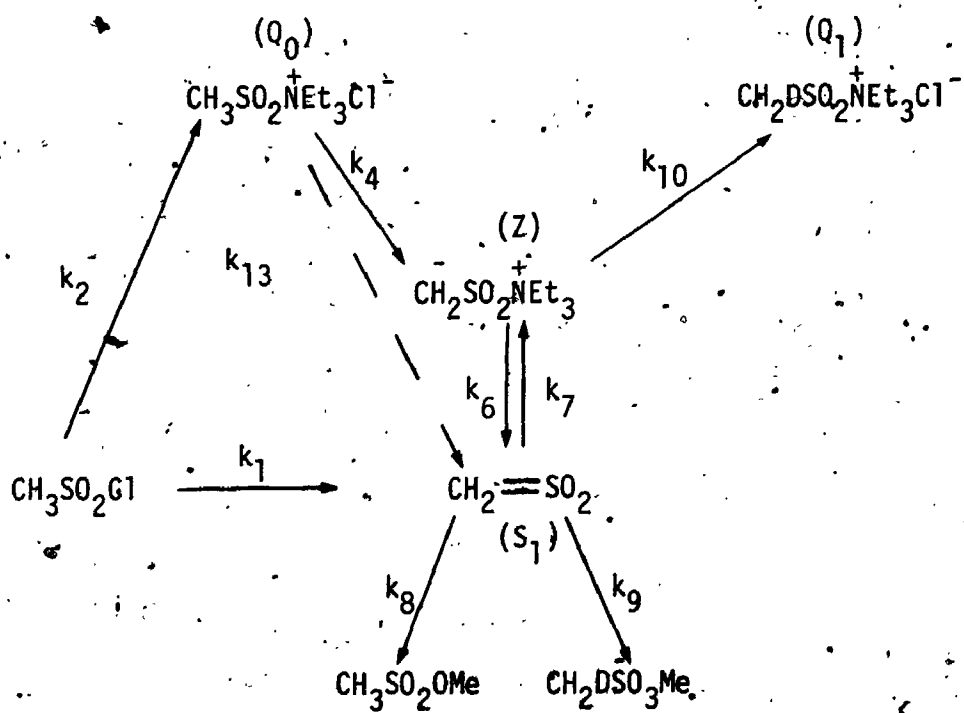
$$\text{rate} = k_2[RSO_2Cl][\text{base}] + k_3[RSO_2Cl][\text{base}][\text{trap}]$$

The observation that some or all of the reaction is zero order in trap required that an intermediate be formed. When the reaction was carried out under conditions in which the third order term gave half of the product and the trap was labelled with deuterium the product was almost exclusively mono-deuterated on the methanesulfonyl portion

of the product. Since the kinetic evidence required the presence of a reactive intermediate and product studies required the presence of a species which would form product with uptake of one and only one deuterium, the sulfene structure was proposed.

The possibility that sulfene formation was taking place via nucleophilic catalysis (k_2 of Scheme 1.8) followed by deprotonation (k_4) to the zwitterion (Z) and collapse of Z to sulfene (k_7) or a one-step elimination (k_{13}) was excluded for the specific case of decalinsulfonyl chloride with triethylamine on the bases of kinetic evidence obtained by these authors.

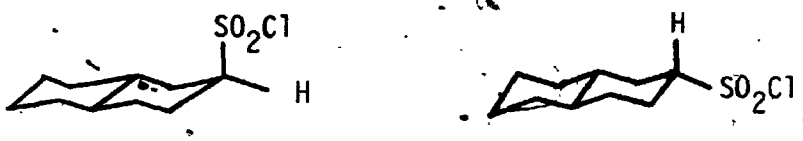
Scheme 1.8



The authors investigated the reaction of triethylamine with equatorial and axial 2-decalinsulfonyl chloride in dimethoxyethane. The rate of reaction between an aliphatic sulfonyl chloride and an amine can be measured equally well by following product formation and by the

formation of free chloride (20) thereby excluding nucleophilic catalysis followed by a slow sequence of step(s) to form sulfene; i.e. k_2 must be slower than k_4 and k_7 and k_{13}. From conformational considerations it can be predicted that 3 will undergo an E2 elimination faster than 4 (Scheme 1.9) and that an S_N2 reaction on 3 will be slower than 4. The authors found that for the triethylamine catalyzed (sulfene forming)

Scheme 1.9

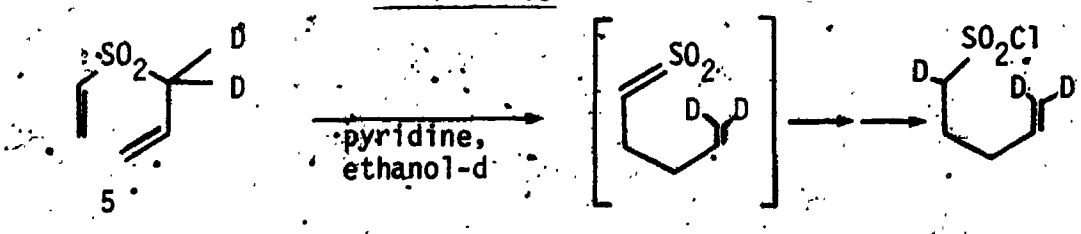


3 4

reactions of 3 and 4 the axial isomer was 71 times faster than the equatorial. For the uncatalyzed hydrolysis (an S_N2) the axial isomer was slower than the equatorial. Since the pattern of relative rates was inverted on going from the noncatalyzed to the catalyzed reaction it was concluded that the rate-controlling step in the triethylamine catalyzed reaction of the decalinsulfonyl chlorides was almost exclusively an elimination process.

In 1971 King and Harding (21) were able to show that allyl vinyl sulfone would give the sulfene shown in Scheme 1.10 as had been suggested earler by Cope (22).

Scheme 1.10



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Preparation of allyl-α,α-d_2 vinyl sulfone (5) and its subsequent rearrangement in pyridine-ethanol-d gave, after treatment with phosphorus oxychloride, 4-pentene-1-sulfonyl chloride-1,5,5-d_3 (6) in which the deuterium of the sulfone had been smoothly transferred to the five position of the product. This indicated that the rearrangement of Scheme 1.4 occurred via a [3,3] sigmatropic shift to give sulfene. The incorporation of one and only one deuterium alpha to the sulfonyl group is also consistent with a sulfene mechanism.

A further demonstration of the likelihood of sulfene occurring as an intermediate was provided in 1973 by the observation of "non-reciprocal kinetic resolution" by King and Sim (23,24). When (+)-camphor-10-sulfonyl chloride ((+)-7) was reacted with racemic menthyl-amine ((±)-8) as shown in Figure 1.1 the diastereomer resulting from the reaction of (+)-7 with (-)-8 was formed in twice the amount as the diastereomer formed from (+)-7 with (+)-8. When racemic 7 was reacted with (-)-8 the two diastereomeric products were formed in equal amounts. It can be shown that these two results require the presence of a slowly formed intermediate which reacts rapidly with the enantiomeric amines at different rates in the second (product-forming) step. These requirements are most reasonably met by a sulfene.

The most satisfactory method of demonstrating the occurrence of a chemical species is its isolation and characterization. The flash thermolysis of chlorosulfonylacetic acid at 640°C and 10^{-3} torr gave products (25,26) which produced methyl mesylate after trapping with methanol at -196° and subsequent warming in 40% yield. The same procedure using hydrogen or deuterium chloride as the trapping agent gave methanesulfonyl chloride and methanesulfonyl-d chloride

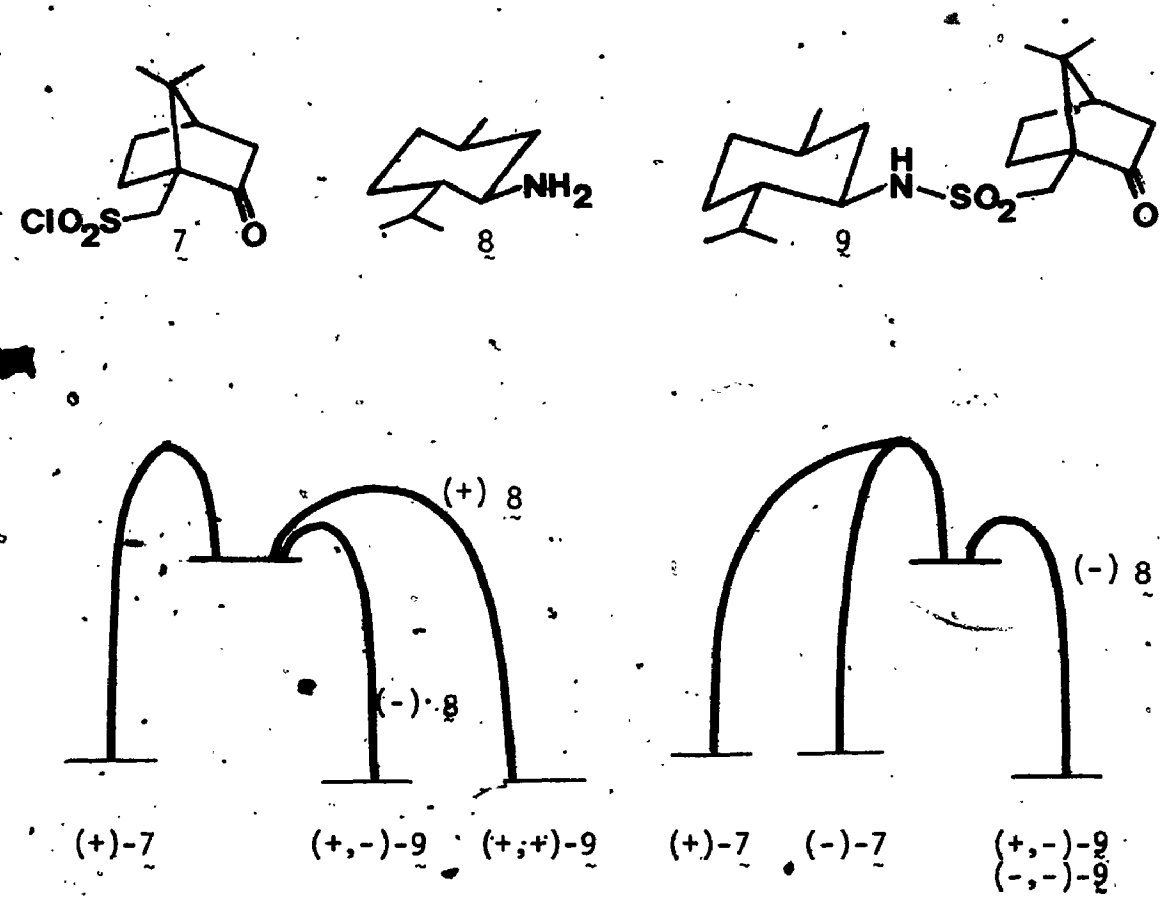
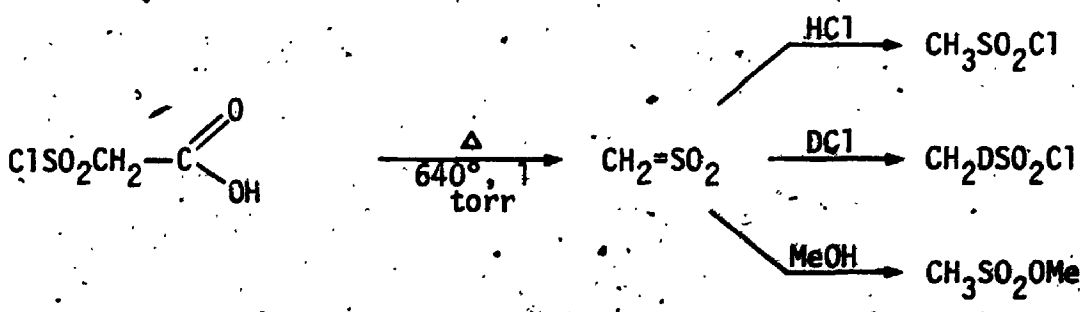


Figure 1.1. Relative Energy Diagrams for the Non-Reciprocal Kinetic Resolution Results with Camphor-10-Sulfonyl Chloride.

respectively (see Scheme 1.11). When the thermolysis product was deposited on a sodium chloride plate at -196°C the infrared spectrum showed five

Scheme 1.11



bands ascribable to sulfene. These were medium strength bands at 3140 and 3040 cm^{-1} assigned to carbon hydrogen stretching, strong bands at 1330 and 1230 cm^{-1} assigned to the sulfonyl moiety and a weak band at 950 cm^{-1}. These bands began to disappear upon warming from -196°C in the presence of the methanol trap to be replaced by bands typical of methyl mesylate. The same bands were observed on thermolysis of methanesulfonic anhydride and photolysis of 3-thietanone 1,1-dioxide (27).

The observations which have been summarized provide good evidence for the existence of sulfenes, one of the key observations being the presence of one and only one deuterium atom in the product obtained in the tertiary amine promoted reaction of an alkanesulfonyl chloride with a deuterated trap such as deuterium oxide. In 1972 however a surprising result was reported by King, Luinstra and Harding (28). When sterically unhindered bases such as trimethylamine were used, the major product was the fully deuterated species $CD_3SO_3^-$ (see Table 1.3). The extent of perdeuteration was correlated with base size. One possible explanation is that unhindered (small) amines are able to do a direct displacement on the sulfonyl group at a rate comparable to sulfene formation. This displacement would result in the formation of a sulfonylammonium ion 10 as shown in Scheme 1.12 which would be able to undergo exchange of hydrogen for deuterium and also, via an elimination reaction, be another route for formation of sulfene. The formation of

Scheme 1.12

$$R_3N + CH_3SO_2Cl \longrightarrow CH_3SO_2\overset{+}{N}R_3Cl^-$$

10

Table 1.3[a]. Multiexchange in the Reaction of Alkanesulfonyl Chlorides with Tertiary Amines and Water or Alcohols.

Entry No.	Sulfonyl Chloride	Base	Trap	Product Composition[b] (%) d_0	d_1	d_2	d_3
1.	$MeSO_2Cl$	Quinuclidine	D_2O	1.8	13.1	21.9	63.1
2.	"	DABCO	"	1.3	16.1	22.8	59.8
3.	"	Me_3N	"	1.8	25.6	24.7	48.0
4.	"	Me_2EtN	"	4.8	71.4	17.6	6.2
5.	"	$MeEt_2N$	"	4.8	92.0	2.5	0.8
6.	"	Et_3N	"	9.6	89.8	0.5	0.0
7.	"	Bu_3N	"	6	94	0	0[c]
8.	"	DABCO	MeOD	0	15	25	60[c]
9.	$EtSO_3Cl$	"	D_2O	5.5	81.4	13.1	-
10.	$PhCH_2SO_2Cl$	Et_3N	"	2.5	95.6	1.9	-
11.	"	DABCO	"	2.8	88.6	8.6	-
12.	"	"	" (small excess)	4.5	93.0	2.5	-
13.	"	"	Bu^tOD	6.3	58.1	35.6	-
14.	p-NO_2-$PhCH_2SO_2Cl$	Et_3N	D_2O	5.7	88.4	5.9	-
15.	"	DABCO	"	2.7	20.7	76.6	-
16.	CH_3SO_2Cl	$BuND_2$	-	20.2	79.8	-	-

a: From du Manoir (30).

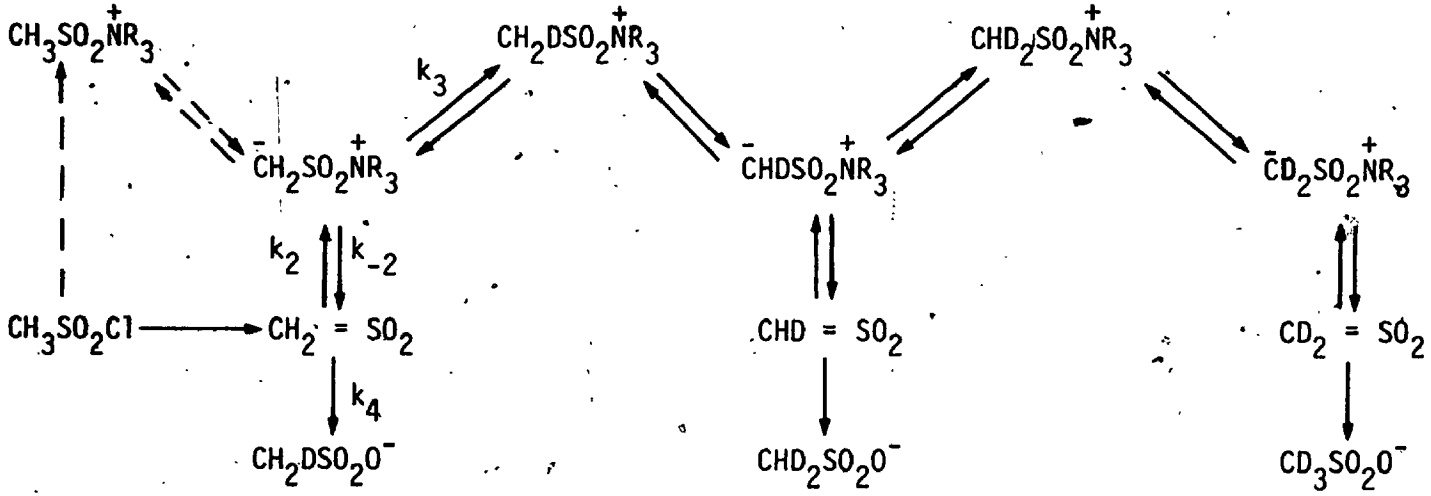
b: Deuterium distribution of the sulfonyl methyl or methylene group of the sulfonic acid or ester product. The sulfonic acids were converted to the sulfonyl chlorides to facilitate mass spectrometric analysis.

c: Estimated by nmr.

this type of salt had, of course, been proposed by Truce and Campbell (19) to compete with sulfene formation by elimination.

Two other mechanisms for multiexchange were excluded by King, Luinstra and Harding. Exchange via the conjugate base of sulfene fails to account for the observed base size effect and the formation of a sulfonylammonium ion (see Figure 1.2) in a one-step reaction from the sulfene was described as requiring a highly unlikely variation in kinetic isotope effects from one base to another.

In order to distinguish between the E2 elimination on methanesulfonyl chloride to form sulfene and the direct displacement reaction by the amine on the sulfonyl group, Luinstra (31) studied the change in rate of sulfene formation with the change in size of the amine base used. Luinstra found that a linear free energy relationship existed between the rate of reaction of methanesulfonyl chloride with tertiary amines in dimethoxyethane and their basicity as measured by the ability of the amine to form an ion pair with 2,4-dinitrophenol in the same solvent. No correlation with base size was found. On the basis of this result the formation of multideuterated produce was proposed to occur by the mechanism of Figure 1.2 where the reactions indicated with dashed arrows were not occurring. In this mechanism multiexchange results from generation of the zwitterion by attack of amine on sulfene. The observation that bulky amines gave less multiexchange was consistent with this mechanism since it is reasonable to assume that zwitterion formation becomes less rapid relative to sulfene trapping and/or decomposition of the zwitterion to the sulfene becomes faster, as the size of the amine increases.



a: Rate constants (k) are pseudo-first-order.

b: From King, Luinstra and Harding (28).

Figure 1.2. The Mechanism of Multiexchange in the Reaction of Methanesulfonyl Chloride with Tertiary Amines and Deuterium Oxide[a,b].

However, the observation of significant amounts of non-deuterated product in the base catalyzed hydrolysis or alcoholysis of alkanesulfonyl chlorides (see for example entries 6 and 16 in Table 1.3) suggests that a direct displacement mechanism may participate to some extent. Dilution of the isotopic pool as the reaction proceeds cannot account for such large yields of non-deuterated product even assuming large isotope effects. Entry 16 of Table 1.3, where the product of the reaction of 60.2 mmoles of 95% isotopically pure n-butylamine-d_2 with 3.22 mmol methanesulfonyl chloride is 20% non-deuterated, is an excellent illustration of this possibility as the bulk of the non-deuterated produce must arise from direct displacement. In other work King, Sim and Li (24) found that the products obtained in the reactions of (+)-camphor-10-sulfonyl chloride and (+)-camphor-10-sulfonyl-10-d_2 chloride with (-)-menthylamine in methylene chloride was consistent with 3 and 10% respectively, of the reaction occurring by direct displacement.

In 1975, King and du Manoir (29) reported the synthesis of a number of trialkyl(methylsulfonyl)ammonium fluorosulfates. These salts when reacted under Luinstra's conditions gave multi-exchanged product (see Table 1.4) showing that the sulfene multiexchange scheme could be entered by way of the sulfonylammonium ion. Although the reaction medium was observed to split into organic and aqueous phases in the multi-exchange reactions, du Manoir was also able to carry out a semi-quantitative analysis of the labelling patterns obtained for the salts in terms of the simplified scheme shown in Figure 1.3. The analysis was performed using a number of assumptions which were:

1. deuterium isotope effects for the exchange reactions would be small. Hence $k_H = k_D = k_e$ and $k_{-H} = k_{-D} = k_{-e}$ where k_e and k_{-e}

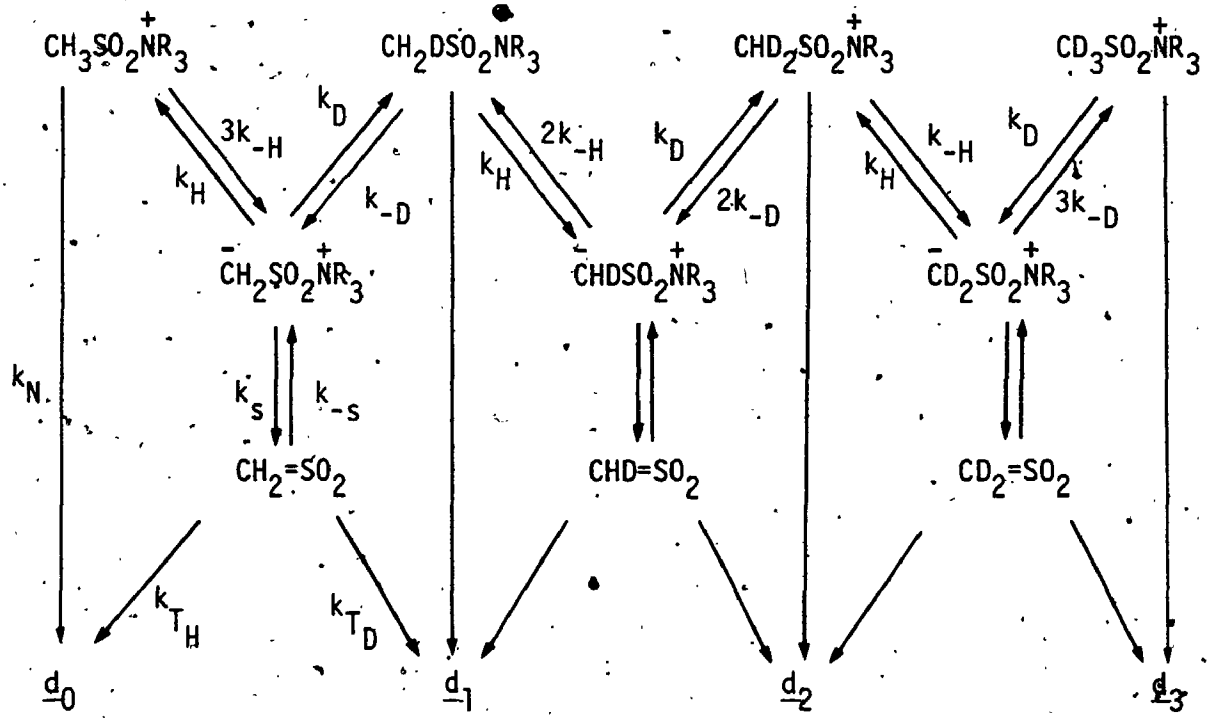
Table 1.4. Multiexchange Reactions with Tertiary Amines and Deuterium Oxide in DME[a].

Substrate	Base	Product Composition[a] (%) d_0	d_1	d_2	d_3
$MeSO_2Cl$	Me_3N	1.8	25.6	24.7	48.0
"	Me_2EtN	4.8	71.4	17.6	6.2
"	$MeEt_2N$	4.8	92.0	2.5	0.8
"	Et_3N	9.6	89.8	0.5	0.0
$MeSO_2\overset{+}{N}Me_3FSO_3^-$	Me_3N	1.3	5.3	29.2	64.2
$MeSO_2\overset{+}{N}Me_2EtFSO_3^-$	Me_2EtN	3.2	9.9	34.7	52.2
$MeSO_2\overset{+}{N}MeEt_2FSO_3^-$	$MeEt_2N$	7.4	40.1	28.4	24.1

a: du Manoir (30).

b: Deuterium distribution of the sulfonyl methyl of the product. The products were converted to the sulfonyl chlorides to facilitate mass spectrometric analysis.

Figure 1.3. Mechanism of Multiexchange in the Reactions of the Trialkyl(methylsulfonyl)ammonium Fluorosulfonate Salts[a,b]



a: Rate constants (k) are pseudo-first-order.

b: From du Manoir (30).

represent the rate of proton or deuteron uptake for the zwitterion and the rate of proton or deuteron removal for the sulfonylammonium salts respectively.

2. the sulfene-zwitterion equilibrium was fast allowing the reaction from the zwitterions to the products to be represented as one step processes. This overall rate was assigned a rate constant of k_T.
3. the ratio of active hydrogen to active deuterium (n) was constant during the reaction.
4. a sulfene trapping isotope effect of two was estimated.

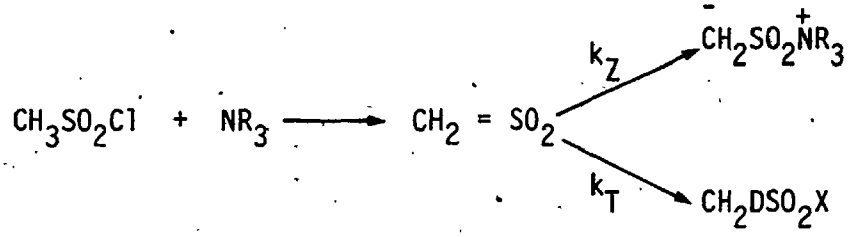
The calculated labelling pattern obtained for the salts is shown in Table 1.5 along with the results calculated for methanesulfonyl chloride. Comparison of these results with the experimental results listed in Table 1.4 show that there is a close correspondence (or fit) between them. When the calculation was attempted with either $k_N = 0$ or $k_T = 0$ a good fit could not be obtained. This was taken to suggest that sulfene trapping and nucleophilic displacement (on the salt species) were both taking place during the sulfene multiexchange reaction. From the data given for the salt reactions an increase in base size from trimethyl- to diethylmethylamine gave smaller calculated values for k_e/k_T and k_{-e}/k_T. For the sulfonyl chloride reactions a rate constant, k_Z, was defined to describe the capture of sulfene by base to form a zwitterion (see Scheme 1.13). For these reactions k_e/k_T, k_{-e}/k_T and k_Z/k_T all decreased in value as the base increased in size. Intuitively these trends are quite reasonable. Although the calculations do not rigorously prove that the mechanism is correct, the close fit between the experimental data and the calculated results when combined with

Table 1.5. Calculated Deuterium Distributions for Multiexchange with Deuterium Oxide in Dimethoxyethane[a]

Substrate	Base	n	k_Z/k_T	k_e/k_T	k_{-e}/k_N	Product Deuterium Distribution (%) d_0	d_1	d_2	d_3
CH_3SO_2Cl	NMe_3	20	6	12	35	1.8	26.0	23.3	48.8
"	$NEtMe_2$	31	1	2	5	4.9	71.5	15.6	9.1
"	NEt_2Me	36	0.17	1.5	1	4.8	91.9	2.6	0.7
$CH_3SO_2\overset{+}{N}Me_3FSO_3^-$	NMe_3	17		22	100	1.1	8.6	24.8	65.6
$CH_3SO_2\overset{+}{N}Et_2MeFSO_3^-$	$NEtMe_2$	18		12	14	3.6	15.5	28.6	52.4
$CH_3SO_2\overset{+}{N}Et_2MeFSO_3^-$	NEt_2Me	24		2.5	7	7.5	39.3	32.5	20.7

a: du Manoir (30).

Scheme 1.13



previous observations indicates that this mechanistic scheme is consistent with the experimental evidence.

As mentioned previously the multiexchange experiments performed by du Manoir for the salts and by Luinstra for methanesulfonyl chloride were not performed under homogeneous reaction conditions. Both workers observed phase separation immediately after the substrate was added to the solution of base and deuterium oxide in DME.

The formation of a two-phase system during the multi-exchange reactions of Luinstra and du Manoir is apparently a salting-out effect. This results in the formation of a heavier aqueous layer consisting of the salts and a solvent shell. This aqueous phase would have a higher local concentration of deuterium than present in the bulk solution which can be expected to increase multiexchange. Other effects which are difficult to assess are any possible differences in D_2O and H_2O solubilities in DME which could affect local concentrations of active deuterium and variations in the ratio of free base and protonated base resulting from phase separation.

The remainder of this chapter will discuss the reactions of three methylsulfonylammonium fluorosulfates and of methanesulfonyl chloride with tertiary amine bases in a deuterium oxide-dimethoxyethane based solvent system which was designed to provide a buffered homogeneous reaction solvent of essentially constant composition to examine the

sulfene multiexchange reaction. Since there are indications that the sulfene multiexchange manifold could be entered as a result of direct displacement on an alkanesulfonyl chloride the investigation to be described will also assess the relative importance of this process.

1.2 Results and Discussion

In this study a series of multiexchange reactions were performed in a deuterium oxide-dimethoxyethane based solvent system. This system was buffered using carbonate-bicarbonate and monitored using a standard pH electrode. The conditions of the reaction were such that pseudo-first order conditions were maintained. For each tertiary amine base used two substrates were subjected to multiexchange. These were the trialkyl(methylsulfonyl)ammonium fluorosulfate whose alkyl groups correspond to those of each base used and methanesulfonyl chloride. For one base, trimethylamine, the multiexchange was performed at two different pH' values (see below). Although the exact experimental procedure is given in the experimental section of this chapter a general outline of the chosen procedure and a summary of the results will be presented at this point.

a) The Multiexchange Reaction Conditions and the Results Obtained

The ability of the carbonate-bicarbonate to maintain pseudo-first order conditions in free amine base was monitored using a standard pH electrode. The "pH" values recorded are simply pH meter readings made following conventional standardization with an aqueous buffer

with no attempt to find true pD values corrected for the dimethoxyethane content. The observed meter readings are referred to herein as pH' values. The equilibrium constants so determined are termed pK_a'. These pK_a' values were obtained by plotting the titration curve using the data presented in the experimental section and taking the half neutralization point as the pK_a'. The values obtained, along with the aqueous pKa, are shown in Table 1.6. A titration curve of carbonate in the same solvent system was also determined. From examination of this curve the best buffering region was found to be between pH' of 10.00 and 10.80.

In order to perform a multiexchange experiment the reaction system was prepared as described in the experimental section of this chapter. For reactions using trimethylamine the addition of amine was performed volumetrically in a cold room at -20°C using the temperature volume correlation of Felsing and Phillips (32). The reaction system, prior to addition of the substrate (4.0 mmol), in acetonitrile (10.0 mL) consisted of 78.6 mL deuterium oxide, 7.0 mL of DME, 80 mmol of total base, 30.00 mmol of potassium carbonate as well as sufficient deuterium chloride to obtain the desired pH'. The average amounts of deuterium chloride necessary for the four solvent systems are shown in Table 1.16 of the experimental section. Using a value of 10.60 as the pK_a' for the deuterio-bicarbonate in the solvent system the ionic strengths of the reaction systems were calculated. The calculations showed less than 5% variation in the ionic strength during a multiexchange reaction. Use of an excess of a non-reactive salt to control the ionic strength was not feasible as

Table 1.6. pK_a' Values Determined in the Deuterium Oxide-Dimethoxyethane Solvent System.

Base	pK_a'	aqueous pK_a[a]
NMe_3	10.31 ± 0.02	9.76
NMe_2Et	10.50 ± 0.02	9.99
$NMeEt_2$	10.76 ± 0.02	10.29
NEt_3	11.18 ± 0.02	10.65

a: Luinstra (31) and references cited therein.

it led to a loss of homogeneity of the reaction system. The problem of maintaining homogeneity also limited the amounts of amine that could be used. An attempt to prepare a solvent system using triethylamine was not successful using a total of 80 mmol of the base. Table 1.7 shows the calculated amounts of free base present during the reactions. Since 4.0 mmol of substrate was used these quantities provide first order reaction conditions in free base.

After the solvent system had been prepared the substrate was added as a solution in acetonitrile. During the addition the pH' was observed to drop until it reached its final reading at the point where the substrate solution appears to have completely mixed. During the remainder of the reaction time (30 min.) the pH' remained constant or increased by up to 0.01 units. In order to check that the reaction time was sufficient a control experiment was performed in which the solution was extracted with ether and after suitable workup the extract examined for the presence of methanesulfonyl chloride. None was found as measured by ^{1}H nmr.

At about the 10 to 15 minute mark an aliquot of the reaction solution was taken. This aliquot was analyzed for protium by the nmr technique described in the experimental section of this chapter. The results are summarized in Table 1.17. As shown, the measured ratio of active deuterium to active hydrogen varied between 77 and 440 with an average value of 200. Estimation of this ratio using the isotopic purities of the deuterium oxide and deuterium chloride solutions and the assumption that 10 mmol of protium are introduced into the reaction medium by the substrate gives a value of approximately 160. This

Table 1.7. Mmol of Free Base Present during the Multiexchange Reactions.

Substrate	Base	pH' (±0.02) initial	pH' (±0.02) final	mmol base initial	mmol base final
$MeSO_2\overset{+}{N}Me_3FSO_3^-$	Me_3N	10.76	10.67	59.2	55.6
$MeSO_2Cl$	"	10.76	10.51	59.2	53.2
$MeSO_2\overset{+}{N}Me_3FSO_3^-$	above	10.23	10.14	36.3	32.3
$MeSO_2Cl$	"	10.23	10.08	36.3	29.6
$MeSO_2\overset{+}{N}Me_2EtFSO_3^-$	Me_2NEt	10.76	10.67	51.6	47.6
$MeSO_2Cl$	"	10.76	10.61	51.6	45.2
$MeSO_2\overset{+}{N}MeEt_2FSO_3^-$	$MeNEt_2$	10.73	10.67	38.6	35.9
$MeSO_2Cl$	"	10.73	10.58	38.6	31.8

suggests that the nmr technique gave results of the correct order of magnitude. However the wide range of values determined for even repetitions of the same multiexchange experiment (see Table 1.18 in the same section) indicated that the values obtained were not precise enough to constitute a reliable method of determining this parameter.

After the multiexchange reaction system had been stirred for 30 minutes the solution was worked up by evaporation of the solvents until a dry white powder containing the product methanesulfonate salts was obtained. This was converted to methanesulfonyl chloride in a 20-30% overall yield using PCl_5 as described in the experimental section. A control experiment indicated that the low yields obtained were not due to incomplete reaction but a result of the workup.

The choice of the workup procedure was dictated by the method used to determine the relative amounts of non, mono, di and trideuterio product obtained from the multiexchange. This was done by measuring the relative heights of the m/e 79, 80, 81 and 82 peaks in a mass spectrometer. These peaks correspond to the CH_3SO_2, CH_2DSO_2, CHD_2SO_2 and CD_3SO_2 mass fragments respectively. The m/e 82 peak was found to contain a variable contribution to its intensity due to the presence of $^{31}P^{16}O^{35}Cl$. This is an artifact of the workup, specifically the use of phosphorus pentachloride. The presence of this peak was confirmed by an exact mass measurement of the peak that could be split off of the m/e 82 signal when the spectrum was run at high resolution (greater than 2000 at the 10% overlap level). After several multiexchange samples had been run it was observed that the intensity of this peak depended on the efficiency of the aqueous washing of the

organic phase obtained from the phosphorus pentachloride reaction with the multiexchanged products. Efficient washing, until the pH of the wash water was greater than four, would usually prevent the appearance of this POCl signal. However, to be assured of reliable results, the mass spectra were run at a resolution greater than 2000 since the calculated resolution necessary to remove this contribution to the m/e 82 signal was 1230.

The mechanics of the mass spectroscopy are described in the experimental section and the computer program used to correct for natural abundance of the various isotopes is presented in Appendix 3. These will not be discussed at this point. However a summary of the results and a discussion of experimental errors will be presented now since the amount of experimental error will affect the interpretation of the results.

For each multiexchange experiment the ms analysis was performed by scanning through the m/e 79 to 82 region (a "trace") at least 4 times. In addition, for a number of experiments, the sample was analyzed a second or even a third time over a several-week period. A typical set of ms results for a multiexchange experiment is shown in Table I.8. The data for this experiment show that the variation in the labelling patterns calculated for the individual traces is of the order of the variation of the average compositions obtained upon reanalysis of the sample. The same type of data for the remainder of the multiexchange experiments are given in the experimental section. Table 1.9 presents the labelling patterns obtained for all the multiexchange experiments and reports the number of times a sample was resubmitted. In cases where the

Table 1.8. Typical Results for the Analyses of the Product from a Multiexchange Reaction[a].

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	79	80	m/e 81	82	D_0	D_1	D_2	D_3
1st m.s. analyses (8000 resolution)								
1	6.5	70.0	9.0	123.5	3.1	33.7	3.7	59.4
2	6.5	60.6	8.5	119.0	3.4	31.3	3.8	61.6
3	8.0	80.0	10.5	139.0	3.4	33.9	3.8	58.9
4	9.0	63.0	8.0	138.5	4.1	29.0	3.1	63.8
Average composition (standard deviation)					3.5 (0.4)	32.0 (2.3)	3.6 (0.3)	60.9 (2.2)
2nd m.s. analysis (8300 resolution)								
1	9.0	99.0	10.5	143.0	3.5	38.1	3.3	55.1
2	8.5	89.0	10.0	132.0	3.6	37.4	3.5	55.5
3	7.0	81.0	9.0	120.0	3.3	37.6	3.4	55.7
4	7.0	81.5	9.0	120.0	3.2	37.7	3.4	55.6
Average composition (standard deviation)					3.4 (0.2)	37.7 (1.5)	3.4 (0.2)	55.5 (1.3)
Average for all m.s. analysis (standard deviation)					3.5 (0.3)	34.8 (1.6)	3.5 (0.2)	58.2 (0.9)

a: data shown were for the multiexchange reaction of methanesulfonyl chloride with trimethylamine at a pH of 10.76.

Table 1.9. Summary of Multiexchange Results Obtained in Deuterium Oxide - Dimethoxyethane.

Substrate	Base	pH' (±0.02)	Percentage Compositions Obtained[a] (standard deviation)				No. of Analyses Obtained
			D_0	D_1	D_2	D_3	
$MeSO_2\overset{+}{N}Me_3\overset{-}{F}SO_3$	Me_3N	10.73	1.1	1.4	11.6	86.0	1
			1.2	1.4	11.5	85.9	1
$MeSO_2Cl$	Me_3N	10.73	4.5	41.0	4.3	50.2	1
			2.8	60.3	1.5	35.4	1
			3.5	34.8	3.5	58.2[b]	2
			(0.3)	(1.6)	(0.2)	(0.9)	
			4.0	44.0	2.7	49.3	3
			(0.3)	(1.0)	(0.3)	(0.9)	
			4.2	39.7	3.4	52.7	2
			(0.5)	(0.6)	(0.2)	(0.6)	
			4.5	46.5	2.3	46.7	1
$MeSO_2NMe_3FSO_3^-$	Me_3N	10.23	0.4	4.4	7.0	88.1	3
			(0.0)	(0.3)	(0.4)	(0.5)	
			0.6	2.7	8.0	88.6	2
			(0.1)	(0.5)	(1.0)	(1.2)	
$MeSO_2Cl$	Me_3N	10.25	8.9	46.7	1.6	42.7	1
			8.5	47.3	1.6	42.6	1
$MeSO_2NEtMe_2FSO_3^-$	$EtMe_2N$	10.74	0.7	4.6	12.5	82.2	3
			(0.7)	(0.7)	(0.6)	(0.9)	
			0.4	3.6	12.9	83.1	2
			(0.0)	(0.4)	(0.5)	(0.6)	
$MeSO_2Cl$	$EtMe_2N$	10.75	0.9	49.2	4.0	45.9	1
			1.1	50.6	4.0	44.3	2
			(0.4)	(1.8)	(0.6)	(1.4)	
			1.0	49.8	5.0	44.2	3
			(0.2)	(1.1)	(0.7)	(1.5)	
$MeSO_2NEt_2MeFSO_3^-$	Et_2MeN	10.73	2.0	24.6	23.7	49.6	1
			1.9	28.3	22.8	47.0	1
			2.0	29.0	23.7	45.5	2
			(0.1)	(0.5)	(0.5)	(0.6)	
$MeSO_2Cl$	Et_2MeN	10.73	2.1	70.2	11.8	15.9	1
			1.3	74.8	11.1	12.8	3
			(0.3)	(0.3)	(0.2)	(0.2)	
			1.4	76.8	8.7	12.9	3
			(0.3)	(0.6)	(0.6)	(0.5)	
			1.1	70.8	10.8	17.3	3
			(0.2)	(0.9)	(0.6)	(0.9)	

a: see footnote a of Table 1.10 for a discussion of the estimated precision of these results.
b: see Table 1.8.

sample was reanalyzed the compositions given are the ones resulting from averaging the results obtained from each sample analysis, for example the fifth set of data in Table 1.9 is the average from both ms analyses of Table 1.8. Comparison of the variation between the two average compositions of Table 1.8 with the variation in the results for the six repetitions of the reaction of $MeSO_2Cl$ with Me_3N at pH' 10.73 shown in Table 1.9 indicates that the errors resulting from repetition of the multiexchange was larger than the errors inherent in the mass spectrostopy. This trend can also be observed by comparing the standard deviations given in Table 1.9 for experiments whose sample was analyzed more than once with the standard deviations of the averaged results of all the experiments as shown in Table 1.10. From these observations it was concluded that the major portion of the variation in results was due to differences between the samples and not due to the mass spectrometry.

b) Qualitative Examination of the Results of the Multiexchange Experiments

Before a detailed examination of the multiexchange results is made, a qualitative assessment of the data in terms of the proposed mechanism (Figure 1.4) is appropriate. To facilitate the discussion the results summarized in Table 1.10 are presented as line graphs in Figure 1.5.

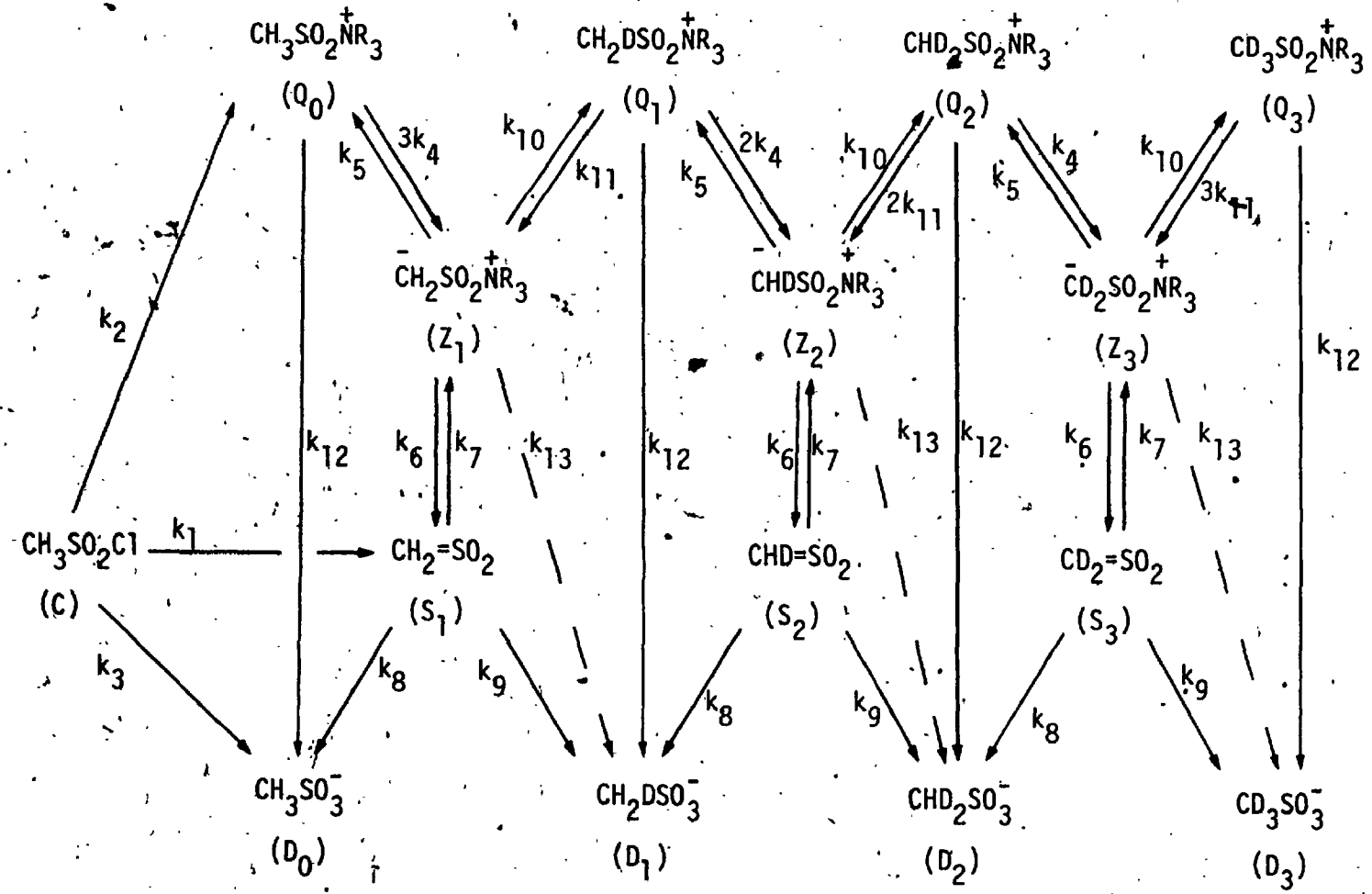
The proposed reaction mechanism is based on that used by King, Luinstra and Harding (28) to rationalize the appearance of multi-exchanged product from the reaction of methanesulfonyl chloride with

Table 1.10. Summary of Averaged Multiexchange Results Obtained in Deuterium Oxide - Dimethoxyethane.

Substrate	Base	average pH' (±0.02)	Average percentage compositions (standard deviation)			
			D_0	D_1	D_2	D_3
$CH_3SO_2NMe_3FSO_3^-$	NMe_3	10.73	1.1 (0.1)	1.4 (0.1)	11.6 (0.0)	85.9 (0.1)
CH_3SO_2Cl	NMe_3	10.73	3.9 (0.7)	44.4 (8.7)	2.9 (1.0)	48.8 (7.6)
$CH_3SO_2\overset{+}{N}Me_3FSO_3^-$	NMe_3	10.23	0.5 (0.1)	3.6 (1.2)	7.5 (0.7)	88.4 (0.3)
CH_3SO_2Cl	NMe_3	10.25	8.7 (0.2)	47.0 (0.4)	1.6 (0.0)	42.7 (0.1)
$CH_3SO_2NEtMe_2FSO_3^-$	$EtNMe_2$	10.75	0.5 (0.2)	4.1 (0.7)	12.7 (0.2)	82.6 (0.6)
CH_3SO_2Cl	$EtNMe_2$	10.75	1.0 (0.1)	49.9 (0.7)	4.4 (0.6)	44.8 (1.0)
$CH_3SO_2NEt_2MeFSO_3^-$	Et_2NMe	10.75	2.0 (0.1)	27.2 (2.4)	23.3 (0.6)	47.5 (1.7)
CH_3SO_2Cl	Et_2NMe	10.75	1.5 (0.4)	73.2 (3.2)	10.6 (1.3)	14.7 (2.3)

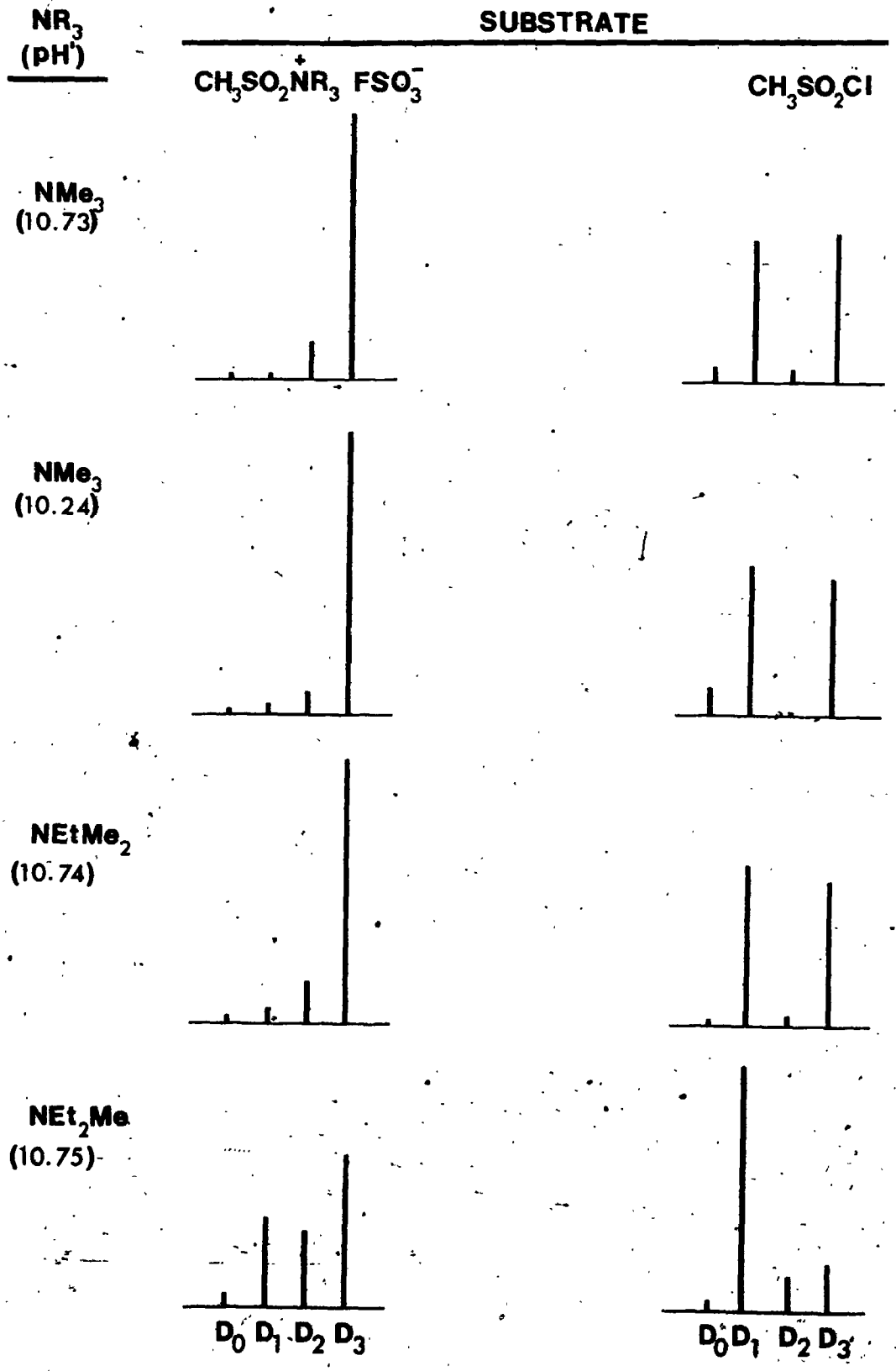
a: The data listed for the individual experiments in Table 1.9 were used to estimate a lower and upper limit to the average percentages shown above. For the nondeuterated products (D_0) the estimated lower limit is D_0-1 and the estimated upper limit is D_0+1. For the mono, di and trideuterated products the limits associated with each value are estimated to be ±3 for monodeuterated product, ±2 for dideuterated product and ±3 for trideuterated product. For the mono and trideuterated products from the reaction of methanesulfonyl chloride with Me_3N at pH' 10.7 the lower and upper limits to the values appear to be much larger. For this reaction the estimated limits are about ±10 and ±15 respectively. For example, actual value for the amount of nondeuterated product for the reaction of trimethyl(methylsulfonyl)ammonium fluorosulfate at pH' 10.73 was estimated to lie between 0.1% and 2.1%.

Figure 1.4. Proposed Multiexchange Mechanism for the Reactions of Trialkyl(methylsulfonyl) ammonium Fluorosulfonate Salts and Methanesulfonyl Chloride[a].



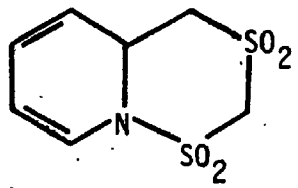
a: Rate constants are pseudo-first-order.

Figure 1.5. Observed Deuterium Distributions for Multiexchange with Deuterium Oxide in Dimethoxyethane



tertiary amines and deuterated traps. The mechanism shown in Figure 1.4 also contains two additional processes; direct attack by trap on the sulfonyl chloride (k_3) and displacement of the amine portion of the methylsulfonylammonium salt (k_{12}).

When the multiexchange reaction is performed using the sulfonyl chloride as the starting material three possibilities can be envisaged. These are sulfene formation via elimination (k_1), formation of a methylsulfonylammonium salt (k_2) and a displacement by the trap to give nondeuterated product (k_3). The second process (k_2) is the one postulated by Truce and Campbell (19) to compete with sulfene formation via elimination. After its formation, the sulfene can be trapped to give nondeuterated (k_8) or monodeuterated product (k_9). The sulfene generated via k_1 could also be attacked by free base to produce the zwitterion, $\bar{C}H_2SO_2\overset{+}{N}R_3$ (k_7). Evidence that this process is a reasonable one, at least for organic solvents, has been obtained by Grossert (33) who obtained a heterocycle 11 from the reaction of methanesulfonyl



11

chloride with pyridine and triethylamine. Although the mechanism of this reaction has not been established, one reasonable route is that sulfene, generated by reaction of methanesulfonyl chloride with triethylamine, is trapped by pyridine to form the zwitterion which then traps a second sulfene to give a second zwitterion that cyclizes to

form 11. In other words sulfene is capable of being trapped by a tertiary amine in an organic medium and hence k_7 is not necessarily neglible. Further evidence for zwitterionic intermediates formed by trapping of sulfene has been obtained by King and Harding in experiments showing the effect of base size on the stilbene - thiobenzoyl S-oxides ratio from reaction of phenylmethanesulfonyl chloride with amines (34). This zwitterion can then be protonated (k_5), deuterated (k_{10}) or revert to sulfene (k_6). Further reactions from the methylsulfonylammonium ion formed by deuteration of the zwitterion can then lead to perdeuterated products.

When the reaction begins from one of the methylsulfonylammonium salts the first step is either production of the zwitterion by deprotonation (k_4) or formation of the nondeuterated product by a nucleophilic displacement (k_{12}). That the latter reaction is a reasonable one was shown by du Manoir who observed that as the size of the alkyl groups on the salt increased the amount of nondeuterated product produced in the reactions with amine in D_2O-DME also increased (see Table 1.4) and argued that this increase would not result if the salts produced product solely by a sulfene trapping mechanism. Du Manoir also observed that $CH_3SO_2Et_2\overset{+}{N}MeFSO_3^-$ with pyridine and p-toluidine gave 63% mesyl methanesulfonamide (a sulfene product) plus 30% methanesulfonamide (a sulfene or a displacement product) while p-toluidine alone gave 96% methanesulfonamide. Since the bases have similar pK_a this suggests that p-toluidine reacts by nucleophilic displacement to some extent. After zwitterion formation the reaction pathways for the salt becomes the same as for the sulfonyl chloride.

The trend observed by du Manoir of an increase in nondeuterated product with an increase in size of the alkyl groups on the salts was also observed in this work. The trend, although real, was less marked than that of du Manoir (compare the D_0 values of Table 1.10 to those of Table 1.4).

The results displayed in Figure 1.5 show that there is a dramatic difference between the labelling pattern obtained from the sulfonyl chloride and that from the salt. For example for the reactions of these substrates with diethylmethylamine the salt gives only 27% monodeuteration while the sulfonyl chloride gives 73%. If the sulfonyl chloride was producing sulfene exclusively via nucleophilic catalysis ($\xrightarrow{k_2}$ $\xrightarrow{k_4}$ $\xrightarrow{k_6}$) the labelling patterns from both starting materials would be identical. Thus on the basis of a qualitative analysis alone, it is apparent that nucleophilic catalysis by the tertiary amine cannot be the exclusive mechanism for sulfene formation in the reaction of a tertiary amine with an aliphatic sulfonyl chloride.

The results also show that as had been observed earlier by Luinstra and du Manoir there is an increasing tendency towards multiexchange as the steric bulk of the base is reduced. This is observed for both the salt series and the sulfonyl chloride. For reactions starting from the salt this trend indicates that k_6 has a significant value with respect to k_{10} since it is reasonable to expect a negligible base size effect in the protonation-deprotonation reactions of the salt and the zwitterion. This is good evidence

that the zwitterion collapses to sulfene.

c) Analysis of the Results of the Multiexchange Reactions Using the Computer Program FINDK

The results of the multiexchange reactions summarized in Table 1.10 were analysed in a more systematic manner by applying the computer program described in Appendix 2. The remainder of this section will describe the approach and the results obtained.

i) General Approach, Assumptions and Conditions

If the concentration of active hydrogen in the reaction system is assumed to be zero the labelling patterns can be described by a set of 5 equations which make use of the following rate constant ratios:

$$x = k_4/k_{12} \qquad H = 1/I = k_{11}/k_4$$

$$a = k_7/k_9 \qquad d = k_{10}/k_6$$

$$u = k_3/k_1 \qquad v = k_2/k_1$$

and the following relationship which relates the rate of deuterated product formation to deuteration for the zwitterion (k_{10}/k_{13}):

$$y = d(a + 1).$$

In these equations (see below) the symbol D_0^T will be used to define the total amount of nondeuterated product (the methanesulfonate anion) and D_1^T, D_2^T and D_3^T the total amounts of the three labelled products. For the multiexchange reaction starting from the salt the equations that interrelate the amounts of each of the four products may be derived as described in Appendix 1 and are summarized as follows:

$$D_0^T = \frac{1}{3x}(D_1^T + D_2^T + D_3^T) \qquad (1)$$

$$D_1^T = \left(\frac{1}{2x} + \frac{1}{y} + \frac{1}{2xy} + \frac{1}{2yI}\right)(D_2^T + D_3^T) \qquad (2)$$

$$D_2^T = \left(\frac{1}{x} + \frac{1}{y} + \frac{1}{xy} + \frac{1}{yI}\right) D_3^T \qquad (3)$$

For the reaction starting from the sulfonyl chloride the expressions for D_0^T and D_1^T are:

$$D_0^T = \left(u + \frac{v}{3x+1}\right)\left[(a+1)\left(D_1^T + \frac{1}{2x}(D_2^T + D_3^T)\right) - \left(\frac{1}{d} + \frac{1}{2dx} + \frac{1}{2dI}\right)(D_2^T + D_3^T)\right] \qquad (4)$$

$$D_1^T = \left[\frac{1}{2x} + \frac{1}{ad} + \frac{1}{2adx} + \frac{1}{2adI} + \frac{1}{a} + \frac{1}{2ax} + \frac{3xv}{3x+1}\left(\frac{a+1}{a} + \frac{1}{ad} + \frac{1}{2adx} + \frac{1}{2adI}\right)\right] \cdot \frac{(D_2T + D_3T)}{\left(1 + \frac{a+1}{a}\frac{3xv}{3x+1}\right)} \quad (5)$$

Since the pathways become identical for both starting materials after Q_1 (see Figure 1.4) is formed the equations relating D_2^T to D_3^T are the same for the reaction starting from the sulfonyl chloride as for the salt, ie. as in equation 3.

Even though the reaction system was designed to provide a large excess of active deuterium it was found that substitution of the exerimental values into equations 1-5 did not give sensible rate constant ratios. Therefore a solution to the multiexchange system that could incorporate the presence of active hydrogen was sought.

The general approach used consisted of the following sequence of steps:

1. Assume a value of k_4/k_{12} and k_2/k_1.
2. Assign a range of values for k_{10}/k_{13} and k_{11}/k_4. For some runs of the computer simulation a particular value of k_{11}/k_4 was chosen by setting the upper and lower limit of this parameter to the same value.
3. Using k_4/k_{12} and k_2/k_1 find the pair of values of k_{10}/k_{13} and k_{11}/k_4 that produce a calculated labelling pattern closest to the experimental one. During this calculation k_{10}/k_{13} is broken down into k_7/k_9 and k_{10}/k_6. Also a value for k_3/k_1 is calculated.

4. Using k_4/k_{12}, k_2/k_1, k_3/k_1, k_7/k_9, k_{11}/k_4, k_{10}/k_6 with the assumption that k_5/k_{10} equals k_{11}/k_4 and an assumed ratio of active deuterium to hydrogen define a set of twelve relative rate constants (k_1 to k_{12}).
5. Calculate the product distribution for the rate constants from step 4.
6. Compare the calculated product distribution with the experimental and based on this comparison, adjust the experimental results to the values one would have expected if there was no active hydrogen present during the reactions.
7. Using the adjusted experimental values go back to step 2 and repeat the sequence of steps until no significant further improvement in the fit between calculated and experimental results is found.

A detailed discussion of this approach and the computer program (FINDK) used to perform the calculations is given in Appendix 2.

The experimentally obtained multiexchange results were examined using FINDK. In order to avoid error due to repeated rounding off the computations were performed using at least six significant figures. The data used are given in Table 1.18 of the experimental section. For programming purposes the experimental results from the salt and sulfonyl chloride for a particular base - pH' combination (eg., the data from the salt and sulfonyl chloride for trimethylamine at pH' 10.73) were placed in an eight membered vector labelled E in the program FINDK. The percentage of nondeuterated product from the salt was placed in the first element of the vector, the monodeuterated product in the

second element and the di and trideuterated products in the third and fourth elements respectively. The values from methanesulfonyl chloride were placed in the fifth to eighth elements of E in the same manner.

The calculated multiexchange results generated by the program were compared to the experimental values using the sum of squares of the element by element difference between E and the calculated values which were stored in the vector M. The equation used was

$$SSQ = \sum_{i=1}^{8} (M(i) - E(i))^2$$

This parameter, SSQ, was used as a relative measure of the ability the rate ratios to generate the experimental results under the assumed conditions - such as the ratio of active deuterium to active hydrogen.

In the search for acceptable solutions the following assumptions and conditions were used:

1. The isotope effect for sulfene trapping was 1.9. This value was determined experimentally and is discussed below.
2. The isotope effects for "protonation" (k_{10}/k_5) and "deprotonation" (k_4/k_{11}) vary between 1.0 and 7.0. Also k_{10}/k_5 equals k_4/k_{11} (for an example see Caldin et al. (34a)).
3. The ratio of active hydrogen to active deuterium is constant during the reaction.

ii) Determination of the Kinetic Isotope Effect for Sulfene Trapping

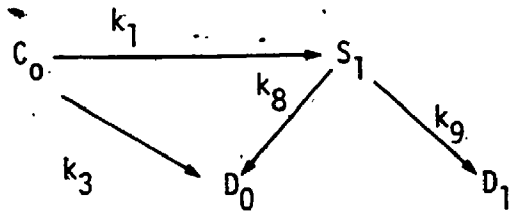
The isotope effect for sulfene trapping (I_T) was measured for the

reaction of methanesulfonyl chloride with triethylamine which eliminated significant multiexchange. When this reaction was carried out in the usual manner for a multiexchange reaction but with 40 mmol of total base, the following product composition was obtained:

D_0	D_1	D_2	D_3
1.7	97.2	0.8	0.1

For this reaction the estimated active hydrogen to deuterium ratio was 0.005. This enables the multiexchange reaction scheme of Figure 1.4 to be simplified to that shown in Scheme 1.14. The experiment was

Scheme 1.14



repeated using a mixture of deuterium oxide and water as the trap. In this experiment the ratio of active hydrogen to active deuterium was 0.927. The results were:

D_0	D_1	D_2	D_3
64.4	35.6	0.0	0.0

Ignoring, for the moment, the contribution to D_0 via the non-sulfene route (k_3) one obtains

$$I_T = \frac{D_0}{D_1} \cdot \frac{1}{0.927} \simeq 1.95$$

This value of I_T was used to estimate the amount of D_0 formed from C_0 in the control experiment starting with deuterium oxide. The approximate amount of D_0 formed from trapping of sulfene ($D_0^{k_8}$) is:

$$D_0^{k_8} \simeq 1.95\ (0.005)(97.2) \simeq 0.948$$

and thus the amount of D_0 formed directly from the sulfonyl chloride ($D_0^{k_3}$) was:

$$D_0^{k_3} \simeq 1.7 - 0.948 \simeq 0.75$$

or approximately 0.75% of the amount of D_0 and D_1 that arose from the sulfene. This value was used to adjust the amount of D_0 obtained in the latter experiment as follows

$$I_T \simeq \frac{(64.4 - 0.75)}{35.6} \cdot \frac{1}{0.927} \simeq 1.9$$

This then, was used as the isotope effect for sulfene trapping (k_8/k_9).

iii) Results Obtained from the Application of the Computer Program FINDK to the Results of the Multiexchange Reactions

The relative rate ratios which were obtained using the computer estimation procedure described in Appendix 2 are summarized in Tables 1.11 to 1.14 for a variety of conditions. The input parameters which were varied from run to run in the simulations were the ratio of k_4/k_{12},

Table 1.11 Computed Results for the Reactions of Trimethyl(methylsulfonyl)ammonium Fluorosulfate and Methanesulfonyl Chloride with Triethylamine at pH' 10.73 in Dimethyoxyethane-Deuterium Oxide.

Entry No.	$\frac{k_4}{k_{12}}$	$\frac{k_{10}}{k_{13}}$	$\frac{k_7}{k_9}$	$\frac{k_{10}}{k_6}$	$\frac{k_{11}}{k_4}$	$\frac{k_2}{k_1}$	$\frac{k_3}{k_1}$	W1	W2	Estimated Results (M)								SSQ
1	75.0	38.8	1.29	16.9	0.993	0.000	0.0387	440	440	0.460	4.36	8.61	86.6	3.92	44.3	4.68	47.1	24.0
2	75.0	24.1	1.32	10.4	0.300	0.000	0.0387	440	440	0.465	5.18	7.69	86.7	3.92	44.3	4.22	47.6	33.2
3	∞	37.0	1.27	16.2	0.987	0.000	0.0365	200	200	0.0369	3.96	8.76	87.2	3.94	44.2	4.73	47.2	23.0
4	75.0	42.9	1.29	18.7	0.991	0.0	0.0365	200	200	0.476	4.06	8.87	86.6	3.94	44.2	4.82	47.1	21.5
5	75.0	34.9	1.31	15.1	0.300	0.000	0.0314	80.0	80.0	0.539	4.00	9.11	86.4	4.09	43.7	4.98	47.2	20.2
6	75.0	34.8	0.769	19.7	0.300	0.300	0.0396	80.0	80.0	0.538	3.99	9.10	86.4	4.10	43.8	4.97	47.1	20.2
7	75.0	34.2	0.141	30.5	0.300	1.000	0.0587	80.0	80.0	0.538	3.98	9.09	86.4	4.11	43.9	4.95	47.1	20.4
8	30.2	62.7	1.29	27.4	0.996	0.000	0.0366	200	200	1.12	3.94	8.56	86.4	3.94	44.2	4.69	47.2	20.9
9	30.0	63.0	1.29	27.6	0.996	0.000	0.0366	200	200	1.13	3.94	8.58	86.4	3.94	44.2	4.69	47.2	20.9
10	30.0	40.0	1.30	17.4	0.300	0.000	0.0365	200	200	1.15	4.41	7.93	86.5	3.94	44.2	4.35	47.5	26.1
11	30.7	108	1.27	47.5	0.993	0.000	0.0299	80.0	80.0	1.12	3.07	9.02	86.8	3.94	43.9	4.91	47.2	16.3
12	30.0	111	1.27	49.0	0.993	0.000	0.0299	80.0	80.0	1.15	2.07	9.00	86.8	3.94	43.9	4.90	47.2	16.3
13	30.0	59.1	1.30	25.7	0.300	0.000	0.0314	80.0	80.0	1.20	3.67	8.93	86.2	4.09	43.8	4.90	47.2	18.6
14	30.0	227	1.28	99.7	1.00	0.000	0.0246	50.0	50.0	1.16	2.51	9.76	86.6	4.04	43.6	5.31	47.1	13.8
15	30.0	231	0.737	132.8	1.00	0.300	0.0288	50.0	50.0	1.16	2.49	9.73	86.6	4.06	43.7	5.27	46.9	14.1
16	30.0	232	0.499	154.7	1.00	0.500	0.0316	50.0	50.0	1.16	2.49	9.72	86.6	4.06	43.8	5.26	46.9	14.3
17	30.0	323	0.113	209	1.00	1.00	0.0385	50.0	50.0	1.16	2.48	9.71	86.7	4.08	43.9	5.24	46.7	14.5
18	75.0	33.9	1.29	14.8	0.300	0.000	0.0365	80.0	200	0.541	4.08	9.21	86.2	3.94	44.2	3.81	48.1	14.3
19	75.0	28.7	1.33	12.3	0.300	0.000	0.0292	200	80.0	0.487	4.53	7.69	87.3	3.88	43.9	5.43	46.8	37.2
20	30.0	178	1.24	79.6	1.00	0.000	0.0363	50.0	200	1.16	2.70	10.1	86.0	3.92	44.3	3.26	48.5	3.94
21	30.0	71.4	1.33	30.7	0.996	0.000	0.0226	200	50.0	1.13	3.68	8.15	87.1	3.84	43.6	6.75	45.6	41.5

Table 1.12. Computed Results for the Reactions of Trimethyl(methylsulfonyl)ammonium, Fluorosulfate and Methanesulfonyl Chloride with Trimethylamine at pH' 10.23 in Dimethoxyethane-Deuterium Oxide.

Entry No.	$\frac{k_4}{k_{12}}$	$\frac{k_{10}}{k_{13}}$	$\frac{k_7}{k_9}$	$\frac{k_{10}}{k_6}$	$\frac{k_{11}}{k_4}$	$\frac{k_2}{k_1}$	$\frac{k_3}{k_1}$	W1	W2	Estimated Results (M)								SSQ
1	75.0	34.5	1.03	17-0	0.416	0.000	0.0931	440	440	0.456	3.48	7.11	89.0	8.72	46.9	3.29	41.1	5.34
2	75.0	31.2	1.03	15.4	0.300	0.000	0.0931	440	440	0.461	4.19	6.52	88.8	8.72	46.9	3.03	41.3	5.43
3	∞	30.0	1.03	14.8	0.421	0.000	0.0913	240	240	0.0306	3.94	6.93	89.1	8.71	46.8	3.21	41.3	5.85
4	∞	29.7	1.03	14.6	0.378	0.000	0.0913	200	200	0.0366	3.91	7.03	89.0	8.71	46.8	3.26	41.3	5.77
5	∞	27.8	1.03	13.8	0.226	0.000	0.0885	160	160	0.0453	3.89	6.84	89.2	8.69	46.7	3.17	41.4	5.70
6	100	31.5	1.03	15.5	0.242	0.000	0.0900	200	200	0.372	3.96	6.75	88.9	8.70	46.8	3.14	41.4	5.20
7	75.0	33.2	1.03	16.3	0.244	0.000	0.0900	200	200	0.484	3.92	6.71	88.9	8.7	46.8	3.12	41.4	5.08
8	75.0	35.8	1.03	17.6	0.300	0.000	0.0900	200	200	0.480	3.80	6.82	88.9	8.70	468	3.17	41.3	5.14
9	66.0	33.8	1.03	16.6	0.144	0.000	0.0885	160	160	0.561	3.87	6.74	88.8	8.69	46.8	3.14	41.4	4.95
10	65.0	34.3	1.03	16.9	0.211	0.000	0.0900	200	200	0.553	3.90	6.70	88.9	8.70	46.8	3.M	41.4	5.04
11	61.0	34.5	1.03	17.2	0.205	0.000	0.0900	200	200	0.587	3.89	6.68	88.9	8.70	46.8	3.11	41.4	5.02
12	61.0	34.8	1.03	17.1	0.144	0.000	0.0885	160	160	0.603	3.84	6.74	88.8	8.70	46.8	3.14	41.4	4.93
13	75.0	52.2	1.02	25.8	0.300	0.000	0.0815	80.0	80.0	0.514	2.94	7.88	88.7	8.64	46.5	3.66	41.2	7.21
14	75.0	52.1	0.551	33.6	0.300	0.000	0.105	80.0	90.0	0.514	2.94	7.87	88.7	8.67	46.6	3.65	41.1	7.32
15	75.0	52.1	0.341	38.8	0.300	0.500	0.120	80.0	80.0	0.514	2.93	7.87	88.7	8.67	46.6	3.65	41.1	7.37
16	75.0	51.9	0.113	46.6	0.300	0.800	0.143	80.0	80.0	0.514	2.93	7.87	88.7	8.66	46.6	3.65	41.1	7.44
17	75.0	50.4	1.01	25.1	0.300	0.000	0.0900	80.0	200	0.516	3.02	7.97	88.5	8.71	46.8	2.64	41.8	2.33
18	75.0	36.7	1.05	17.9	0.300	0.000	0.0814	200	80.0	0.479	3.72	6.73	89.1	8.63	46.4	2.20	40.7	11.9

Table 1.13. Computed Results for the Reactions of Dimethylethyl(methylsulfonyl)ammonium Fluorosulfate and Methanesulfonyl Chloride with Dimethylethylamine at pH 10.75 in Dimethoxyethane-Deuterium Oxide.

Entry No.	$\frac{k_4}{k_{12}}$	$\frac{k_{10}}{k_{13}}$	$\frac{k_7}{k_9}$	$\frac{k_{10}}{k_6}$	$\frac{k_{11}}{k_4}$	$\frac{k_2}{k_1}$	$\frac{k_3}{k_1}$	W1	W2	Estimated Results (M)								SSQ
1	75.0	27.5	1.12	13.0	0.964	0.000	0.00774	440	440	0.466	5.75	10.7	53.1	0.982	49.8	5.63	43.6	10.0
2	75.0	17.1	1.15	7.98	0.300	0.000	0.00812	440	440	0.473	6.91	9.65	83.0	1.02	49.8	5.12	44.0	18.6
3		26.5	1:11	12.5	1.00	0.000	0.000	200	200	0.0509	5.45	11.1	83.4	0.474	50.0	5.83	43.7	8.80
4	75.0	30.4	1.11	14.4	0.992	0.000	0.00513	200	200	0.490	5.39	10.9	83.2	0.982	49.8	5.73	43.5	8.61
5	75.0	18.7	1.14	8.76	0.300	0.000	0.00576	200	200	0.505	6.46	9.87	83.2	1.05	49.8	5.22	44.0	15.4
6	65.0	30.8	1.11	14.6	1.00	0.000	0.000	200	200	0.558	5.43	11.0	82.9	0.473	50.0	5.81	43.7	8.30
7	75.0	23.7	1.12	11.2	0.300	0.000	0.000	80.0	80.0	0.570	5.35	10.7	83.3	1.18	49.5	5.58	43.7	9.24
8	75.0	23.6	0.624	14.5	0.300	0.300	0.000	80.0	80.0	0.570	5.35	10.7	83.3	1.25	49.5	5.58	43.6	9.49
9	75.0	23.6	0.402	20.3	0.300	0.500	0.000	80.0	80.0	0.570	5.35	10.7	83.3	1.36	49.5	5.56	43.6	9.85
10	75.0	23.5	0.166	22.4	0.300	0.800	0.000	80.0	80.0	0.572	5.34	10.6	83.4	1.45	49.6	5.54	43.4	9.95
11	75.0	23.5	0.0468	22.4	0.300	1.00	0.000	80.0	80.0	0.572	5.43	10.7	83.3	1.45	49.5	5.58	43.5	9.95
12	100.0	31.7	1.11	15.1	0.378	0.000	0.000	50.0	50.0	0.490	4.42	11.8	83.3	1.85	48.9	6.09	43.1	8.92
13	88.0	31.7	1.10	15.0	0.331	0.000	0.000	50.0	50.0	0.538	4.42	11.6	83.5	1.86	49.0	6.00	43.2	8.92
14	75.0	22.9	1.11	10.9	0.300	0.000	0.00576	80.0	200.0	0.575	5.59	10.9	83.0	1.05	49.8	4.57	44.6	5.90
15	75.0	19.2	1.15	8.94	0.300	0.000	0.0000499	200	80.	0.504	6.31	9.71	83.5	1.18	49.5	6.25	43.1	21.3

Table 1.14. Computed Results for the Reactions of Diethylmethyl(methylsulfonyl)ammonium Fluorosulfate and Methanesulfonyl Chloride with Diethylmethylamine at pH 10.75 in Dimethoxyethane-Deuterium Oxide.

Entry No.	$\frac{k_4}{k_{12}}$	$\frac{k_{10}}{k_{13}}$	$\frac{k_7}{k_9}$	$\frac{k_{10}}{k_6}$	$\frac{k_{11}}{k_4}$	$\frac{k_2}{k_1}$	$\frac{k_3}{k_1}$	W1	W2	Estimated Results (M)								SSQ
1	75.0	3.08	0.549	1.96	0.265	0.000	0.0121	440	440	0.561	27.3	24.8	47.3	1.51	73.2	8.71	16.6	11.3
2	75.0	3.17	0.546	2.05	0.300	0.000	0.0121	440	440	0.559	27.0	25.1	47.3	1.51	73.2	8.79	16.5	11.9
3	∞	2.94	0.550	1.90	0.225	0.000	0.0086	200	200	0.259	27.5	24.5	47.7	1.55	73.2	8.58	16.7	12.4
4	∞	2.94	0.550	1.90	0.226	0.000	0.0	200	200	0.259	27.5	24.5	47.7	0.70	73.8	8.66	16.8	13.6
5	75.0	3.11	0.547	2.01	0.259	0.000	0.00807	200	200	0.700	27.1	24.9	47.3	1.50	73.2	8.73	16.6	11.0
6	75.0	3.22	0.543	2.09	0.3	0.000	0.00859	200	200	0.696	26.8	25.3	47.2	1.55	73.2	8.82	16.5	11.9
7	30.0	3.18	0.541	2.06	0.178	0.000	0.00804	200	200	1.36	26.5	23.7	48.4	1.50	73.2	8.32	17.0	12.1
8	30.0	3.02	0.293	2.33	0.174	0.200	0.00808	200	200	1.37	27.4	24.1	47.1	1.55	73.2	8.53	16.7	9.18
9	30.0	3.01	0.193	2.53	0.174	0.300	0.00783	200	200	1.37	27.4	24.1	47.1	1.55	73.3	8.52	16.7	9.17
10	30.0	3.01	0.0338	2.91	0.174	0.500	0.00734	200	200	1.37	27.4	24.1	47.1	1.55	73.3	8.51	16.7	9.14
11	75.0	3.35	0.537	2.18	0.3	0.000	0.000	80.0	80.0	1.05	26.2	25.7	47.0	1.74	73.1	8.90	16.3	13.3
12	75.0	3.34	0.277	2.62	0.3	0.200	0.000	80.0	80.0	1.05	26.2	25.7	47.0	1.74	73.1	8.89	16.2	13.2
13	75.0	3.34	0.178	2.83	0.300	0.300	0.000	80.0	80.0	1.05	26.2	25.7	47.0	1.85	73.0	8.88	16.2	13.3
14	75.0	3.33	0.0177	3.27	0.300	0.500	0.000	80.0	80.0	1.05	26.2	25.7	47.0	1.88	73.0	8.87	16.2	13.3

the ratios of active hydrogen to deuterium for the salts (W1) and the sulfonyl chloride (W2), the range of k_{10}/k_{13} to be examined, the range of k_{11}/k_4 to be examined and the ratio k_2/k_1. The output of each simulation were the values of k_{10}/k_{13}, k_7/k_9, k_{10}/k_6, k_{11}/k_4, k_3/k_1, the vector M which contains the predicted labelling pattern and SSQ.

In general the results of the computer simulations for all four systems are similar. In all of the simulations the results obtained (the vector M) are within the estimated experimental errors (see Table 1.10) of the experimental results. As a result, comparison of one simulation to another can only be relative ones. For all four systems there is a trend in the quality of the fits obtained. When a low active deuterium to hydrogen ratio (eg. W1 = W2 = 80) is used a better fit is obtained than when a high value (eg. W1 = W2 = 440) is used. From the results listed, it was observed that each of k_4/k_{12}, k_{10}/k_6 or k_{11}/k_4 do not have a large effect on the fits obtained. As a result, it was not possible to determine values for these three rate ratios for the four systems. In the simulations listed it was observed however, that one parameter, k_7/k_9, is constant for each reaction system when k_2/k_1 was zero. Specifically k_7/k_9 was 1.3 for trimethylamine at pH' 10.73; 1.0 for trimethylamine at pH' 10.24; 1.1 for dimethylethylamine at pH' 10.75; and 0.55 for diethylmethylamine at pH' 10.75. This observation will be used later in the discussion of the extent of nucleophilic catalysis in the reaction of the sulfonyl chloride with the three amines. In the following paragraphs a detailed discussion of the computer simulations for the trimethylamine at pH' 10.73 will be given. At the appropriate points any significant variation of the results of this simulation of this system to those of the other three

systems will be noted.

Table 1.11 shows the computed results for the reactions of trimethyl(methylsulfonyl)ammonium fluorosulfate and methanesulfonyl chloride at pH' 10.73 with trimethylamine. The right hand side of the table gives the estimated labelling patterns for the two starting materials as the vector M in the same manner as has been described for the vector E as well as SSQ which provides a measure of the fit of the calculated values in M with the experimental values (see Table 1.10). The left hand side of the table gives the ratios of rate constants and the active hydrogen to active deuterium ratios (W1 for the salt; W2 for the sulfonyl chloride) which produce the vector M.

Inspection of the results shown in entries 3,4,8 and 9 of Table 1.11 indicates that the value of k_4/k_{12} does not appreciably affect the fit of the computed results to the experimental results. In entry 3 the value of k_4/k_{12} was taken to be infinite, indicating that nucleophilic displacement (k_{12}) on the sulfonyl group of the methylsulfonylammonium salts (the Q_i in Figure 1.5) was not occurring. In entries 8 and 9 k_4/k_{12} was about the minimum possible. This can be calculated using equation 1 in the following form.

$$\frac{k_4}{k_{12}} = \frac{(100 - D_0^T)}{3D_0^T} \qquad (6)$$

For the trimethylamine reaction with the methylsulfonylammonium salt D_0^T was about 1.1% which means that k_4/k_{12} would be about 30. Since equation 6 ignores any formation of D_0 from the trapping of sulfene (k_8 in Figure 1.5) with protium and from any hydrolysis of the salt

before its addition to the multiexchange medium this computation gives only a minimum value of k_4/k_{12}. Even though the relative rate of deprotonation (k_4) to give a zwitterion (Z) is large compared to product formation via nucleophilic displacement (k_{12}), a significant amount of the products could still arise from nucleophilic displacement since the protonation of the salt is reversible. In order to assess the amount of product formation via nucleophilic displacement some sets of parameters that produced "best fits" for a number of the entries of Table 1.11 were converted to rate constants and used as input to a modified version of the MUTLT12 subroutine of FINDK. The modification to the subroutine consisted of additional statements which allowed the subroutine to calculate the relative amounts of total product formed by direct displacement on the sulfonyl halide (k_3), trapping of sulfene by protium (k_8), trapping of sulfene by deuterium (k_9) and by nucleophilic displacement (k_{12}) on the sulfonylammonium salts. For the trimethylamine system at a pH' of 10.73 the parameters of entry 9, where k_4/k_{12} was assumed to be 30.0, require that the amount of products formed via nucleophilic displament (k_{12}) in the reaction of the salt was approximately 44% of the total (ie.; of D_1, D_2, D_3 plus D_4). For the sulfonyl chloride the amount was 24% of the total product. When k_4/k_{12} was assumed to be 75.0 the amounts were 16 and 9% respectively. As expected when k_4/k_{12} was infinite no product was formed via this route. Unfortunately, since the fit between the experimental data (Table 1.10) and the calculated data does not appreciably change when k_4/k_{12} is varied from the lower limit of 30.0 to the upper limit of ∞ it is not possible to estimate a value for this ratio. Although the "fit" between the experimental and calculated data is not very dependent

on k_4/k_{12}, a change in k_4/k_{12} does affect k_{10}/k_6. As k_4/k_{12} increases k_{10}/k_6 decreases (see entries 3, 4, 8 and 9 of Table 1.11). This can be rationalized by postulating that as product formation by k_{12} is lessened, one must increase the opportunity for product formation from the sulfene to obtain a good fit to the experimental data.

Another feature of the computed results obtained was the effect of changing the assumed values of the active deuterium to hydrogen ratio (W1 and W2). Entries 11 and 12, when compared to entries 8 and 9 suggest that, on the basis of a lower SSQ, a lower effective ratio of active deuterium to hydrogen than those measured by nmr or estimated from the nominal purity of the reagents may be present during the reaction. The effective ratio of active deuterium to hydrogen may be lower than that of the bulk of the reaction due to mixing rate effects. Rys (35) has discussed chemical selectivity disguised by mixing rate effects. For example, Rys reports that in the bromination of resorcinol by molecular bromine in methanol the ratio of the 2,4-dibromo- to 4,6-dibromo products- which specifically depends on the resorcinol/ resorcinolate ratio, ie. pH - depended upon the stirring speed used. This implied that the protons released during the reaction were not diffused rapidly enough into the bulk solution relative to protonation of the resorcinolate ion. In general, Rys estimates that any chemical event that occurs in less than 0.01 - 1 s can be affected by mixing-rate effects.

In the case of the multiexchange system one could postulate that a protium concentration gradient is formed, the excess protium near the substrate being that abstracted by the base. In order to ascertain whether the multiexchange reaction was fast or slow with respect to

mixing the reaction was performed in the usual manner and a quenching solution was added. The addition of the substrate took 6 s and this was immediately followed by addition of the quenching solution whose addition required 10 s to complete. After stirring the the usual time the quenched reaction was worked up to give methanesulfonyl chloride. This was analyzed by ms to give the results shown in Table 1.15. The results obtained from the multiexchanges performed without quenching are also presented in the table for comparison. The results for the quenched experiment differ somewhat from the nonquenched experiments but the ratios of trideuterated to dideuterated product are essentially the same for both the quenched and nonquenched multiexchange experiments. Since one would expect a noticeable change in these values upon dilution of the deuterium content of the medium this suggests that the di- and trideuterated products in the quenching experiments were formed before addition of the quenching solution, ie. during the 6 second addition of the reagent to the multiexchange medium. By comparing the sum of D_2 plus D_3 for the two quenching experiments to the sum D_2 plus D_3 of the appropriate normal multiexchanges one can attempt to approximate the percentage of completion of the reaction. For the reaction of the salt one obtains about 70% and for the sulfonyl chloride 60%. Thus it appears that the major portion of product formation occurs during the 6 second addition. Since formation of di and trideuterated products require at least 5 chemical events and only the portion of the substrate that was added first is in the multiexchange medium for the full six seconds, it is entirely possible that mixing rate effects are occurring as judged by Rys' criterion of less than a 0.01 to 1 second lifetime for a chemical event to be susceptible to mixing rate effects. However,

Table 1.15. Results Obtained from the Quenching of the Reactions of Methanesulfonyl Chloride and Trimethyl(methylsulfonyl)ammonium Fluorosulfate with Trimethylamine at pH' of 10.7 with Excess Water.

Reaction type	Percentage Compositions Obtained							
	Trimethyl(methylsulfonyl)ammonium fluorosulfate				Methanesulfonyl chloride			
	D_0	D_1	D_2	D_3	D_0	D_1	D_2	D_3
Quenching	8.0	19.7	8.0	64.6	17.2	52.8	1.6	28.3
Normal Multiexchange[a] (standard deviation)	1.1 (0.1)	1.4 (0.1)	11.6 (0.0)	85.9 (0.1)	3.9 (0.7)	44.4 (8.7)	2.9 (1.0)	48.8 (7.6)

a: from Table 1.10.

even though invoking a mixing-rate phenomenon leads to an improvement in the fit between the experimental and calculated results, it is apparent from the closeness of the fit at the lowest active deuterium to hydrogen ratio measured experimentally (~80) that the results do not require this explanation.

The possibility that mixing rate effects could be occurring also suggests that each of the two reactants for each system may experience a different ratio of active deuterium to hydrogen (ie. $W1 \neq W2$). This was briefly investigated using the program FINDK. For each reaction system, the simulations was carried out with W1 = 80 and W2 = 200 for one run and W1 = 200 and W2 = 80 for another. For the trimethylamine system at pH' 10.73 the results (see entries 18 and 19 on Table 1.11) showed that a better fit was obtained with W1 < W2 suggesting that the salt reacts faster than the sulfonyl chloride and thus is affected more strongly by a mixing-rate effect. This trend was also found for the trimethylamine at pH' 10.24 and dimethylethylamine at pH' 10.75 systems. However this was not the case for the diethylmethylamine system at pH' 10.75. Whether this indicates that the diethylmethyl salt has a smaller likelihood of being affected by a mixing rate phenomenon with respect to the sulfonyl chloride than the other salts is not readily apparent. In any case, as all the fits are adequate within the estimated experimental error to explain the experimental results one can only make note of the possibility that mixing rate effects may differ between the salts and the sulfonyl chloride.

A third feature of the results of Table 1.11 is the effect of k_{11}/k_4 on the fit. This ratio is of course the inverse of the kinetic isotope effect for deprotonation of the trialkylmethylsulfonylammonium salt.

Since the reaction of base with this salt is very fast it was not feasible to obtain a measured value for this parameter. As is illustrated by entries 1 and 2 and by 9 and 10 the effect of changing k_{11}/k_4 on the fit (SSQ) is not large. This means that the approach used in FINDK to estimate "best fits" is unable to provide a best value for k_{11}/k_4.

iv) Nucleophilic Catalysis in the Reaction of Methanesulfonyl Chloride With the Tertiary Amine Bases

As discussed in the introduction to this chapter one of the questions this investigation was designed to answer was, what if any is the extent of nucleophilic catalysis in the reaction of methanesulfonyl chloride with a tertiary amine base? It is clear, from a qualitative comparison of the results obtained from the reaction of the sulfonyl chloride to those obtained from the appropriate methylsulfonylammonium salt that for all of the three amines investigated, nucleophilic catalysis cannot be the predominant process. To evaluate the extent of the participation of nucleophilic catalysis use is made of the observation that the ratio of k_7/k_9 did not vary as the input assumptions for FINDK were varied as long as k_2/k_1 was set to zero. Referring to Figure 1.4 one could predict that an increase in k_2/k_1, which means that more of the sulfonyl chloride would react with the amine by a nucleophilic displacement, should be offset by a decrease in k_7/k_9 to produce the same predicted labelling pattern for the reaction of methanesulfonyl chloride. Of course if k_7/k_9 is decreased for the reaction of the salt and this in turn means that k_{10}/k_6 will have to

be increased.

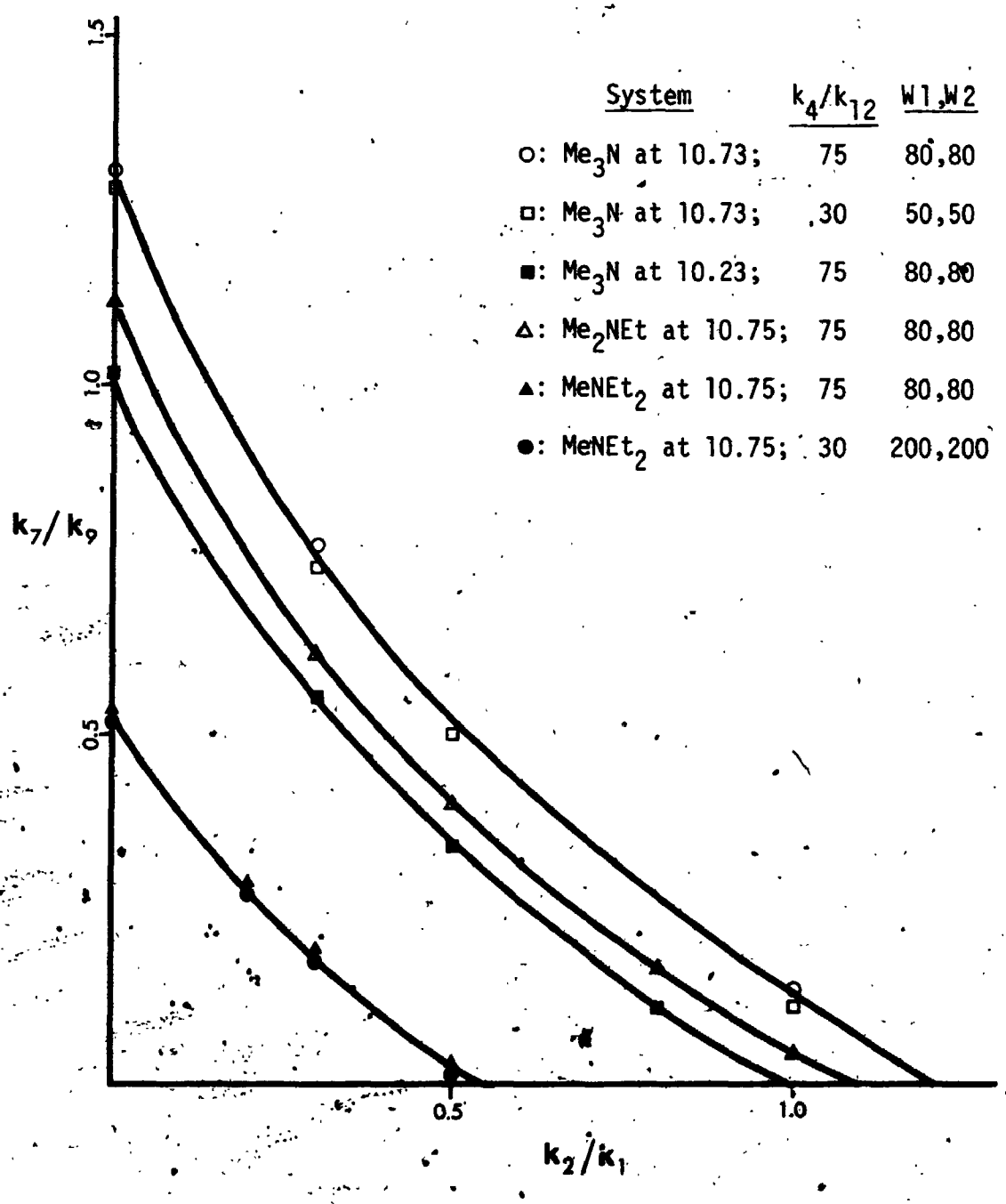
Figure 1.6 graphically summarizes the results of the computer simulations when k_2/k_1 was set to values greater than zero. As k_2/k_1 was increased for a particular set of parameters such as those of entries 5 to 7 of Table 1.11 (k_4/k_{12} = 75, k_{11}/k_4 = 0.3 and the ratio of active hydrogen to deuterium equal to 80) the value of k_7/k_9 decreases. Plotting k_7/k_9 versus k_2/k_1 for a variety of combinations of k_4/k_{12}, k_{11}/k_4, active deuterium to hydrogen ratios, and bases shows that a smooth curve is obtained for each plot. In addition the plots for a particular substrate and pH', such as the two for the reaction with trimethylamine at 10.73, are superimposable regardless of the choice of k_4/k_{12} etc. Thus it is possible to take the value of k_2/k_1 when k_7/k_9 is zero as the maximum k_2/k_1 for each substrate at a specified pH'. The maximum k_2/k_1 values were:

Reaction System	Maximum k_2/k_1
Me_3N at 10.7	1.2
Me_3N at 10.2	1.0
Me_2NEt at 10.7	1.1
$MeNEt_2$ at 10.7	0.55

The trend in these maximum k_2/k_1 values is that a relatively bulkier amine has a lower k_2/k_1 than a less bulky one. This is intuitively correct as it is expected that changes in the steric bulk of the base should affect nucleophilic displacement more strongly than elimination to form sulfene.

To obtain an estimate of the maximum proportion of sulfonylammonium

Figure 1.6. Plots of k_7/k_9 Versus k_2/k_1 Using Data From Computer Simulations.



ion that could arise in the reaction of methanesulfonyl chloride with triethylamine we make use of a further piece of information which gives an estimate of the relative rates of nucleophilic attack by Et_3N versus Et_2NMe. Expressing the rate constant for the disappearance of methanesulfonyl chloride (k_0) as a summation of rates one obtains:

$$k_0 = k_1 + k_2$$

$$\text{or} \quad k_0 = k_1 + Rk_1.$$

R is a proportionality constant equal to k_2/k_1. This allows the relative rate data for nucleophilic reactions of amine bases to be used to estimate R for other amines if one assumes that k_1 is not significantly affected by the differences in base strength of the amines used and that one can assume that k_3 is sufficiently small so that the direct substitution with the trap is negligible. Data obtained by Skonieczny (38) shows that triethylamine is 6.3 times less nucleophilic than diethylmethylamine in the attack on C-2 of ethenesulfonyl chloride in water containing 0.2% DME. Adjustment of the R value (k_2/k_1) of diethylmethylamine by this factor gives a maximum value of R equal to 0.087 for triethylamine. This would suggest then, that in the reaction of methanesulfonyl chloride with triethylamine about 8.0% of the reaction proceeds via the nucleophilic catalysis route. It should be pointed out that the assumptions used to obtain this value are such that this value must be regarded as a maximum. For example, using the k_7/k_9 intercept in Figure 1.6 to estimate k_2/k_1 for diethylmethylamine

requires that none of the sulfene generated be trapped by the amine to form the zwitterion and thereby be a source of perdeuterated product. That this is probably not so can be concluded from the previously mentioned results obtained by Grossert (33) and by King and Harding (34) that in organic solvents at least, k_7 is a reasonable process.

A further point suggesting that 8.0% of nucleophilic catalysis is a conservative maximum is the evidence indicating that steric effects accompanying attack at sulfonyl sulfur are actually greater than those found on carbon in the reaction with ethenesulfonyl chloride. For the ethenesulfonate reaction, attack at the β carbon is four times faster for pyridine than 2-picoline (34). For the nucleophilic catalysis of benzenesulfonyl chloride methanolysis the reaction with pyridine is about 100 times faster than with 2-picoline (36).

A third reason for believing that 8.0% nucleophilic catalysis with triethylamine is maximal derives from the fact that in the above estimation k_1 was assumed to be the same for Et_2NMe and Et_3N. The available evidence indicates that the rate of sulfene formation depends strongly on base strength. This indicates that k_1 for Et_3N is larger than k_1 for Et_2NMe and hence the proportion of nucleophilic catalysis calculated for Et_3N must be smaller.

At this point it is worth noting that for the reaction of diethylmethylamine with methanesulfonyl chloride in benzene-acetonitrile the results of Chapter 2 indicate that the maximum k_2/k_1 could not be greater than 1, which, as a result of the same estimation as carried out above, required that for an organic solvent the maximum extent of nucleophilic catalysis with triethylamine is 15%.

1.3 Conclusions

From the experimental results obtained, and the computer analysis of these results in terms of the mechanism shown in Figure 1.4 it can be concluded that:

1. the experimental results (see Figure 1.5) clearly show that the reaction of methanesulfonyl chloride with a tertiary amine cannot be going primarily by nucleophilic catalysis as the product distribution obtained from the salt was quite different from that obtained from the sulfonyl chloride.
2. the mechanism proposed (Figure 1.4) is consistent with the experimental results.
3. the maximum ratio of nucleophilic catalysis to sulfene formation for the reaction of methanesulfonyl chloride in a buffered aqueous system ranges from 1.2 for trimethylamine to 0.55 for diethylmethylamine.
4. the extent of nucleophilic catalysis in the reaction of methanesulfonyl chloride with triethylamine is estimated to be less than 8.0%.

1.4 Experimental

Proton nuclear magnetic resonance (nmr) spectra were recorded on a Varian T-60 spectrometer. Mass spectra and precise mass determinations were obtained on a Varian MAT 311A instrument.

Solvents were obtained from Fisher Scientific. Dimethoxyethane (DME) was dried by distillation from calcium hydride and acetonitrile by distillation from phosphorus pentoxide. Trimethylamine and triethylamine were obtained from Eastman Chemicals, dimethylethylamine from ICN-K&K Laboratories and diethylmethylamine from Aldrich Chemicals. Except for trimethylamine which was used as supplied, the amines were dried by distillation from lithium aluminum hydride. Deuterium oxide used for exchange experiments was obtained from Merck, Sharp and Dohme, Montreal, minimum isotopic purity 99.7%. Concentrated deuterium chloride, minimum isotopic purity 99%, was obtained from the same source. Anhydrous potassium carbonate was obtained from Fisher Scientific and stored in an oven at 120 C. Methanesulfonyl chloride was obtained from Eastman Chemicals and redistilled prior to use. The trimethyl, dimethylethyl and diethylmethyl(methylsulfonyl)ammonium fluorosulfates were prepared by the method of du Manoir (30).

General Procedure for the Reaction of Methanesulfonyl Chloride or the Quaternary Methylsulfonylammonium Fluorosulfonate Salts with Tertiary amines in Deuterium Oxide

The reaction medium was prepared by dissolving potassium carbonate (4.146 g, 30.00 mmol) in deuterium oxide (60 mL) and dimethoxyethane (7.0 mL) in a Radiometer V520 Titration Jacket

equipped with a water cooling jacket and a ground glass cap which has three openings for the introduction of reagents and to accommodate a Radiometer GK2401B electrode attached to a Radiometer model 25 pH meter equipped with a scale-expander so that pH (or pH') could be measured to 0.01 of a pH unit. During the reaction the openings in the ground glass cap were closed with cork stoppers to prevent evaporation of the volatile amines and the reaction temperature was maintained at 20.0 C (± 0.1) by circulation of water from a Haake FJ constant temperature bath through the water jacket of the vessel.

To the solution prepared above the appropriate amount of amine (80 mmol) was added while stirring with a magnetic stirrer. Trimethylamine was added by pipetting the appropriate volume (eg. 6.94 ml at -22 C) using the temperature-volume relationship determined by Felsing and Phillips (22) with stirring in a cold room. After the addition this solution was warmed to 20.0 C using the constant temperature bath. Ethyldimethylamine (5.85 g) was added by weight and diethylmethylamine (9.76 mL) was added by volume. These were added to the solution at 20 C. The solution was titrated to a pH' value ~0.03 units higher than the desired one for the reaction with standardized deuterium chloride in deuterium oxide which had been diluted to approximately 6 M for ease of handling. The amount of DCl solution used was recorded and a further amount of deuterium oxide added to the reaction medium so that the total amount of D_2O was 78.6 ml. This method resulted in a drop in the pH' to the desired value. The average amounts of DCl used to titrate the four reaction mixtures to the appropriate pH' values are given in Table 1.16.

Table 1.16. Average Number of Millimoles Deuterium Chloride Used to Prepare the D_2O - DME Multiexchange Reaction Systems.

Base	pH'	Average No. of mmols (standard deviation)
Me_3N	10.73	34.1 (1.9)
Me_3N	10.23	62.1 (6.7)
Me_3NEt	10.75	49.2 (3.7)
$MeNEt_2$	10.75	56.4 (4.6)

At this point the pH' reading was recorded and 4 mmol of the substrate in dry acetonitrile (10 mL) was added to the reaction solution. The addition time was 6 seconds. The following amounts of substrate were used, methanesulfonyl chloride (0.31 ml), trimethyl(methylsulfonyl)ammonium fluorosulfonate (0.95 g), ethyldimethyl(methylsulfonyl)ammonium fluorosulfonate (1.00 g), and diethylmethyl(methylsulfonyl)ammonium fluorosulfonate (1.06 g). In the case of the trimethyl salt gentle heating, temperature not exceeding 35°C, was necessary to ensure rapid solution in acetonitrile before addition to the reaction medium.

After the addition of reagent the pH' value was recorded. For the methanesulfonyl chloride addition the pH' value dropped by approximately 0.15 units and for the addition of the salts the value dropped by approximately 0.08 units. The reaction mixture was allowed to stir for 0.5 h after addition to ensure complete reaction. It was noted that the pH' reading of the reaction mixture was essentially constant during this period, rising no more than 0.01 units. During this stirring period an aliquot of the reaction mixture was taken for analysis of the active deuterium to hydrogen ratio by nmr. The nmr technique used is described in the next section along with a summary of the results obtained (Table 1.17).

The reaction was worked up by evaporation of the liquid at 0.1 torr to give a dry white powder to which methylene chloride (30 mL) and phosphorus pentachloride (3.0 g) was added. The suspension was stirred for 2 h and filtered through fluted filter paper into a separatory funnel. The organic phase was washed with 50 mL aliquots

Table 1.17. Data Obtained from nmr Analysis for Active Hydrogen in Selected Multiexchange Experiments.

Multiexchange Results in Table No.	Weight of sample analyzed in grams	Integration value for HOD peak in millimeters (corresponding volume H_2O added in µL)							µL H_2O found (active D/active H)
1.20.5	0.5427	7.0 (0.0)	26.0 (5.0)	41.0 (10.0)	57.5 (15.0)	82.0 (20.0)	94.0 (25.0)		2.0 (160)
1.20.6	0.6386	6.0 (0.0)	20.5 (5.0)	32.0 (10.0)	50.0 (15.0)	64.5 (20.0)	84.0 (25.0)		1.6 (260)
1.20.7	0.5661	5.0 (0.0)	17.0 (5.0)	35.0 (10.0)	45.0 (15.0)	51.0 (20.0)	75.0 (25.0)	83.0 (30.0)	1.0 (340)
1.20.8	0.5723	5.5 (0.0)	19.0 (5.0)	37.0 (10.0)	51.5 (15.0)	67.5 (20.0)	80.5 (25.0)	98.5 (30.0)	1.6 (220)
1.20.9	0.4678	6.5 (0.0)	23.0 (5.0)	47.0 (10.0)	64.0 (16.0)	89.0 (20.0)	116.5 (25.0)		1.3 (220)
1.20.10	0.6162	7.0 (0.0)	19.0 (5.0)	35.0 (10.0)	53.0 (15.0)	66.0 (20.0)	86.0 (25.0)		1.8 (210)
1.20.11	0.6606	6.0 (0.0)	19.0 (5.0)	33.0 (10.0)	44.0 (15.0)	58.5 (20.0)	72.0 (25.0)	81.5 (30.0)	2.5 (160)
1.20.12	0.6734	7.5 (0.0)	23.0 (5.0)	41.0 (10.0)	54.0 (15.0)	72.5 (20.0)	88.0 (25.0)		2.5 (140)
1.20.13	0.4672	11.0 (0.0)	17.5 (5.0)	27.0 (10.0)	34.0 (15.0)	40.0 (20.0)	46.0 (25.0)	63.0 (30.0)	1.3 (220)

Table 1.17. Continued.

Multiexchange Results in Table No.	Weight of sample analyzed in grams	Integration value for HOD peak in millimeters (corresponding volume H_2O added in μL)							μL H_2O found (active D/active H)
1.20.15	0.5264		7.0 (0.0)	24.5 (5.0)	41.0 (10.0)	65.0 (15.0)	81.0 (20.0)	95.0 (25.0)	2.0 (160)
1.20.16	0.5988	6.0 (0.0)	16.0 (5.0)	26.5 (10.0)	35.5 (15.0)	41.5 (20.0)	56.0 (25.0)	63.0 (25.0)	64.0 (30.0) 2.3 (160)
1.20.17	0.5766	5.0 (0.0)	9.5 (5.0)	25.0 (10.0)	32.0 (15.0)	47.0 (20.0)	51.0 (25.0)	65.0 (30.0)	2.5 (140)
1.20.22	0.6381	9.0 (0.0)	23.5 (5.0)	36.0 (10.0)	41.0 (15.0)	48.0 (20.0)	67.0 (25.0)		5.0 (78)
1.20.23	0.580	12.5 (0.0)	31.5 (5.0)	79.5 (15.0)	93.0 (20.0)	108 (25.0)			3.4 (110)
1.20.24	0.5498	7.5 (0.0)	35.0 (5.0)	47.0 (10.0)	98.0 (15.0)	119.0 (20.0)			0.75 (440)
Average W value (standard deviation)									200 (92)

of distilled water with backwashing until the pH of the water wash was greater than four. This washing was essential to minimize the appearance of POCl peaks in the subsequent mass spectral analysis. After drying and filtration the organic phase was evaporated under reduced pressure (water aspirator) to give a 20 to 30% crude yield of methanesulfonyl chloride. The crude product was doubly distilled from bulb to bulb under bench vacuum prior to mass spectral analysis.

As a control experiment 4 mmol. (456 mg) of methanesulfonyl chloride was submitted to the same workup procedure starting from the aqueous washing of the filtrate from the PCl_5 chlorination of the reaction products to give a 36% recovery. In another control experiment a solution of 2 mmol of methanesulfonyl chloride (an assumed yield of 50% for the chlorination) in 30 mL of CH_2Cl_2 was prepared. The solvent was then removed by evaporation in the usual manner to give a 77% recovery of the sulfonyl chloride. These two control experiments indicate that the low yield of methanesulfonyl chloride obtained was mainly due to the washing procedure used to minimize the POCl signal in the mass spectroscopy.

General Method for the Measurement of Active Hydrogen in the Deuterium Oxide-Dimethoxyethane Based Reaction Medium

To determine the hydrogen content of the multiexchange reaction medium a nmr spectrum of an accurately weighed aliquot was obtained and the integral of the HOD signal recorded. Successive portions of water (5 µL) were then added to the aliquot and the integral of the HOD peak measured after each addition. A plot of the magnitude

of the integral of the HOD peak versus the amount of water added was then made and the absolute value of the x-intercept was taken as the amount of water (μL) in the sample. The procedure used is given in detail below for a control sample which approximates the multiexchange reaction medium.

A solution of potassium carbonate (1.0 g), triethylamine (1.5 g), dimethoxyethane (1.8 mL), acetonitrile (2.5 mL), deuterium chloride (1.5 mL, 6.09 M) in deuterium oxide (18.0 mL) was prepared as a mimic of the multiexchange medium. Five samples of this mixture were analyzed for active hydrogen. The values obtained for a 0.5780 g sample of this solution are given below:

μl H_2O added	0.0	5.0	10.0	15.0	20.9	25.0
nmr integral	6.0	27.0	53.5	71.5	109	121

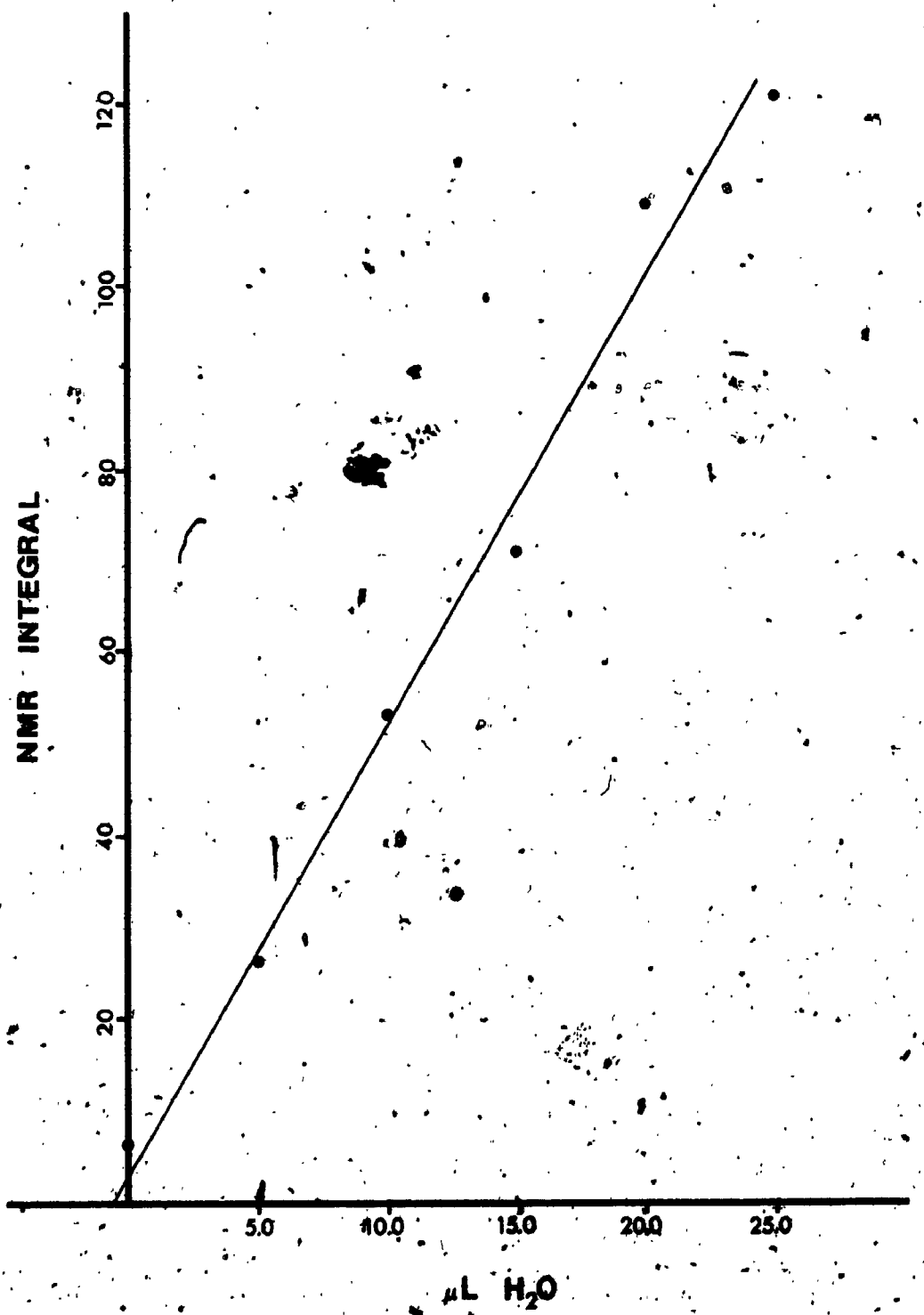
These data were analysed graphically as shown in Figure 1.7. The best least squares line was drawn and the absolute value of the intercept on the volume axis taken as the number of μL of water in the sample. The volume obtained was converted to an active deuterium to active hydrogen ratio (W) using the following formula:

$$W = \frac{\dfrac{\text{wt. analytical sample}}{\text{mol. wt. } D_2O} \times \dfrac{\text{wt. } H_2O \text{ in reaction}}{\text{wt. solution}}}{\text{Volume } H_2O \text{ found in mL} \times \dfrac{\text{density } H_2O}{\text{mol. wt. } H_2O}}$$

$$W = \frac{\text{wt. analytical sample}}{\text{volume } H_2O \text{ found in mL}} \times C$$

$C = 0.65$ for the control sample

Figure 3.7. The Determination of the Active Hydrogen Content of the Multiexchange Medium.



and C = 0.61 for the multiexchange media.

The results of the water analyses for five aliquots of the control sample are:

aliquot no.	wt. aliquot	Vol. H_2O found (μl)	W
1	0.4780	1.0	310
2	0.4265	0.7	400
3	0.4438	1.8	160
4	0.4387	2.0	140
5	0.4647	2.5	120
Average value			230
(standard deviation)			(120)

Mass Spectral Analysis of Deuterated Methanesulfonyl Chlorides: Methods and Results

The mass spectra of the sulfonyl chloride samples obtained from the multiexchange experiments were run at 25 eV and a probe temperature of 100°C. It was found that scanning the m/e 79 to 82 region was most convenient for the analysis of the labelling pattern since the signal due to the molecular ion was weak.

At the 10% peak overlap level a resolution of 1230 is necessary to remove the contribution due to $PO^{35}Cl$ from the signal for CD_3SO_2 at m/e 82. The measurements were carried out at a resolution of 2,000 which ensured that ^{34}S, and ^{18}O were not resolved or between 8,000 and 10,000 which ensured that ^{34}S, and ^{18}O were resolved.

The peak heights for the m/e 79, 80, 81 and 82 peaks were used to

calculate the relative amounts of the labelled products taking into account natural abundance. The values used to calculate the correction factors used were taken from Silverstein and Bassler (37). The correction factors for the low resolution measurements were defined as:

C_1, the percentage of CH_3SO_2 (m/e 79) that appears at m/e 80 due to the presence of ^{13}C, natural abundance ^{2}H, ^{33}S and ^{17}O.

C_2, the percentage of CH_3SO_2 that appears at m/e 81 due to the presence of ^{34}S or ^{18}O.

C_3, the percentage of CH_3SO_2 that appears at m/e 82 due to ^{13}C and ^{34}S appearing in the fragment at the same time.

C_4, C_7 and C_{10} are defined as for C_1 for the CH_2DSO_2, CHD_2SO_2 and CD_3SO_2 fragments respectively.

C_5, C_8 and C_{11} are defined as for C_2 for the CH_2DSO_2, CHD_2SO_2 and CD_3SO_2 fragments respectively.

C_6, C_9 and C_{12} are defined as for C_3 for the CH_2DSO_2, CHD_2SO_2 and CD_3SO_2 fragments respectively.

Thus C_1 = 1.08% + 3(0.016%) + 0.78% + 2(0.04%)

= 1.988%

C_2 = 4.4% + 2(.2%)

= 4.8%

C_3 = 1.08% (4.4%)

= 0.048%

and C_4 = 1.972%

C_5 = 4.8%

C_6 = 0.048%

C_7 = 1.956%

C_8 = 4.8%

C_9 = 0.048%

C_{10} = 1.94%

C_{11} = 4.8%

C_{12} = 0.048%

At high resolution (8,000 to 10,000) the contribution to peak height of ^{34}S is separated from ^{18}O and the correction factors become:

C_1 = 1.988

C_4 = 1.972

C_7 = 1.956

C_{10} = 1.940

with the other eight correction factors equal to zero.

The results shown in Tables 1.18.1 and 1.18.2 were those of a control experiment performed on a natural abundance sample of methanesulfonyl chloride. The measured peak heights and the corrected peak heights are given for both the low resolution and high resolution measurements. As expected the corrected values for the m/e 80, 81 and 82 peaks are equal to zero within experimental error. The absence of a peak at m/e 78 indicates that proton loss, and by analogy deuterium loss, does not affect the reliability of the mass spectra method to determine the labelling pattern of the multiexchange products.

The results obtained from the multiexchange experiments are given in Tables 1.19 and 1.20. Table 1.19 presents the trace number, peak heights and the percentage composition for each trace as well as the average composition for all of the traces obtained for the sample.

Table 1.18.1 Mass Spectral Results from a Natural Abundance Sample of Methanesulfonyl Chloride at 2000 Resolution.

Trace No.	Peak Heights in Millimeters (±0.5)					Corrected Peak Heights in Millimeters[a] (±0.5)			
	m/e					m/e			
	78	79	80	81	82	79	80	81	82
1	0.0	138.0	2.5	6.0	0.0	147.4	-0.2	-0.6	-0.1
2	0.0	137.0	3.0	6.0	0.0	146.3	0.3	-0.6	-0.1
3	0.0	135.5	2.5	6.0	0.0	144.8	-0.2	-0.5	-0.1
4	0.0	136.0	2.5	6.0	0.0	145.3	-0.2	-0.5	-0.1
5	0.0	135.0	2.5	6.0	0.0	144.2	-0.2	-0.5	-0.1

a: calculations performed by hand using the correction factors C_1 = 1.988%, C_2 = 4.8% and C_3 = 0.048% as described in the text.

Table 1.18.2 Mass Spectral Results From a Natural Abundance Sample of Methanesulfonyl Chloride at 8300 to 10,000 Resolution.

Trace No.	Peak Heights in Millimeters (±0.5)					Corrected Peak Heights in Millimeters (±0.5)			
	m/e					m/e			
	78	79	80	81	82	79	80	81	82
1st ms analysis (10,000 resolution)									
1	0.0	114.0	2.0	0.0	0.0	116.3	-0.3	0.0	0.0
2	0.0	112.0	2.5	0.5	0.0	114.1	0.4	0.5	0.0
3	0.0	120.5	2.5	0.0	0.0	122.9	0.1	0.0	0.0
4	0.0	115.0	2.0	0.5	0.0	117.3	-0.3	0.5	0.0
2nd ms analysis (8300 to 10,000 resolution)									
1	0.0	111.5	2.0	0.5	0.0	113.7	-0.2	0.5	0.0
2	0.0	105.0	2.0	0.5	0.0	107.1	-0.1	0.5	0.0
3	0.0	104.0	2.0	0.5	0.0	106.1	-0.1	0.5	0.0
4	0.0	83.5	2.0	0.5	0.0	85.2	0.3	0.5	0.0
5	0.0	89.0	2.0	0.0	0.0	90.8	0.2	0.5	0.0

Table 1.19. Multiexchange Experiments: Isotopic Composition of Products.

Experiment No.: 1.19.1
Substrate: $CH_3SO_2NMe_3FSO_3^-$
Base: Me_3N
pH': 10.73 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (10,000 resolution)								
1	1.5	2.5	20.0	141.0	0.9	1.5	12.1	85.5
2	2.0	2.0	18.0	137.0	1.3	1.2	11.3	86.2
3	1.5	2.0	18.0	132.0	1.0	1.3	11.7	86.0
4	1.5	2.0	15.5	121.0	1.1	1.4	11.1	86.4
Average composition					1.1	1.4	11.6	86.0
(standard deviation)					(0.2)	(0.1)	(0.5)	(0.4)

Table 1.19. Continued

Experiment No.: 1.19.2
Substrate: $CH_3SO_2\overset{+}{N}Me_3FSO_3^-$
Base: NMe_3
pH': 10.73 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
Ist m.s. analysis (10,000 resolution)								
1	1.5	2.0	15.0	116.0	1.1	1.5	11.2	86.3
2	1.0	1.5	12.0	91.0	1.0	1.4	11.4	86.3
3	1.5	1.5	13.0	97.0	1.3	1.3	11.5	85.9
4	1.5	2.0	15.0	105.5	1.2	1.6	12.1	85.1
Average composition					1.2	1.4	11.5	85.9
(standard deviation)					(0.2)	(0.1)	(0.4)	(0.6)

Table 1.19. Continued

Experiment No. 1.19.3
Substrate: CH_3SO_2Cl
Base: Me_3N
pH': 10.72 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st M.S. analysis (10,000 resolution)								
1	7.5	70.0	7.5	85.5	4.4	41.4	3.6	50.6
2	11.5	103.0	13.0	119.5	4.7	42.0	4.5	48.8
3	10.0	95.5	12.5	113.0	4.4	41.7	4.6	49.3
4	10.0	88.0	12.0	118.5	4.4	38.8	4.5	52.3
Average composition					4.5	41.0	4.3	50.2
(standard deviation)					(0.1)	(1.5)	(0.5)	(1.5)

Table 1.19. Continued

Experimental No.: 1.19.4
Substrate: CH_3SO_2Cl
Base: Me_3N
pH': 10.72 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
lst.m.s. analysis (10,000 resolution)								
1	6.0	118.0	6.0	71.0	3.0	59.4	1.9	35.7
2	5.0	122.5	5.0	73.0	2.5	60.3	1.3	35.9
3	6.0	116.5	5.0	62.5	3.2	62.1	1.4	33.3
4	4.0	90.5	4.0	56.0	2.6	59.3	1.5	36.7
Average composition					2.8	60.3	1.5	35.4
(standard deviation)					(0.3)	(1.3)	(0.2)	(1.5)

Table 1.19. Continued

Experiment No.: 1.19.5
Substrate: CH_3SO_2Cl
Base: Me_3N
pH': 10.74 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e 79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8000 resolution)								
1	6.5	70.0	9.0	123.5	3.1	33.7	3.7	59.4
2	6.5	60.5	8.5	119.0	3.4	31.3	3.8	61.6
3	8.0	80.0	10.5	139.0	3.4	33.9	3.8	58.9
4	9.0	63.0	8.0	138.5	4.1	29.0	3.1	63.8
Average composition (standard deviation)					3.5 (0.4)	32.0 (2.3)	3.6 (0.3)	60.9 (2.2)
2nd m.s. analysis (8300 resolution)								
1	9.0	99.0	10.5	143.0	3.5	38.1	3.3	55.1
2	8.5	89.0	10.0	132.0	3.6	37.4	3.5	55.5
3	7.0	81.0	9.0	120.0	3.3	37.6	3.4	55.7
4	7.0	81.5	9.0	120.0	3.2	37.7	3.4	55.6
Average composition (standard deviation)					3.4 (0.2)	37.7 (1.5)	3.4 (0.2)	55.5 (0.3)
Average for all m.s. analyses (standard deviation					3.5 (0.3)	34.8 (1.6)	3.5 (0.2)	58.2 (0.9)

2

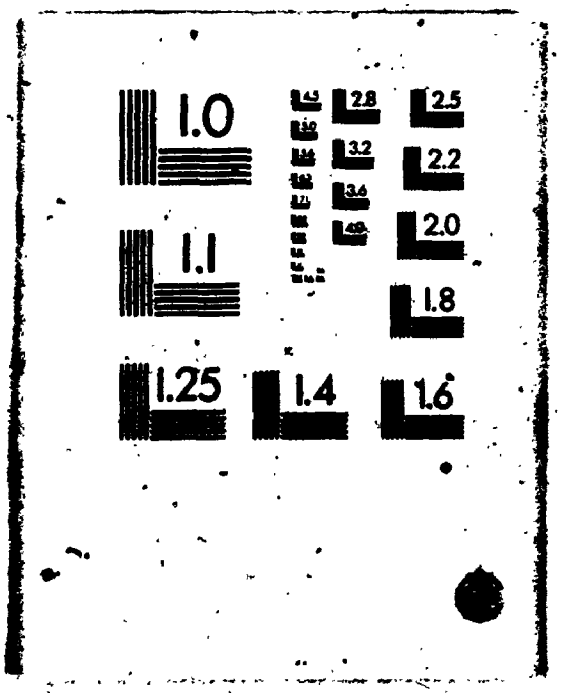


Table 1.19. Continued

Experiment No.: 1.19.6
Substrate: CH_3SO_2Cl
Base: Me_3N
pH': 10.74 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	9.0	100.5	9.0	123.0	3.8	47.9	2.9	51.4
2	9.0	99.5	8.5	122.5	3.8	41.9	2.7	51.6
3	9.0	111.0	8.5	120.0	3.7	45.1	2.6	48.7
4	9.0	111.0	8.5	129.0	3.5	43.5	2.5	50.5
Average composition (standard deviation)					3.7 (0.1)	43.1 (1.5)	2.7 (0.2)	50.5 (1.3)
2nd m.s. analysis (8000 resolution)								
1	10.0	114.0	9.0	122.5	4.0	45.0	2.7	48.4
2	12.0	140.0	10.5	148.0	3.9	45.5	2.5	48.1
3	10.0	116.0	9.0	132.0	3.8	43.8	2.5	49.9
4	10.5	116.0	9.0	126.0	4.1	44.7	2.6	48.6
Average composition (standard deviation)					3.9 (0.1)	44.8 (0.7)	2.6 (0.1)	48.7 (0.8)
3rd m.s. analysis (8000 resolution)								
1	9.0	97.0	7.0	105.0	4.2	44.9	2.4	48.6
2	11.5	100.0	7.5	108.0	5.1	44.4	2.5	48.0
3	9.5	97.0	8.5	111.0	4.2	43.3	2.9	49.5
4	8.5	87.0	7.0	94.5	4.4	44.5	2.7	48.4
5	10.0	93.0	9.5	104.0	4.7	43.3	3.6	48.4

cont'd

Table 1.19 Continued

Experiment No.: 1.19.6 (continued)

Trace No.	Peak heights in millimeters (0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
Average composition (standard deviation)					4.5 (0.4)	44.1 (0.7)	2.8 (0.5)	48.6 (0.6)
Average for all m.s. analysis (standard deviation)					4.0 (0.3)	44.0 (1.0)	2.7 (0.3)	49.3 (0.9)

Table 1.19. Continued

Experiment No.: 1.19.7
Substrate: CH_3SO_2Cl
Base: Me_3N
pH: 10.72 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	10.0	96.0	9.5	118.0	4.3	41.4	3.3	51.0
2	11.5	96.5	11.0	125.5	4.7	39.8	3.8	51.7
3	10.0	88.0	9.5	114.0	4.6	40.0	3.5	51.9
4	10.0	91.0	9.0	121.0	4.4	39.7	3.2	52.8
Average composition (standard deviation)					4.5 (0.2)	40.2 (0.8)	3.4 (0.3)	51.8 (0.8)
2nd m.s. analysis (8300 resolution)								
1	9.5	96.0	10.0	132.0	3.9	39.1	3.3	53.7
2	9.5	90.0	9.5	120.5	4.2	39.5	3.4	52.9
3	9.0	94.0	9.5	128.0	3.8	39.4	3.2	53.6
4	8.5	85.0	8.5	117.0	3.9	39.0	3.1	53.8
Average composition (standard deviation)					3.9 (0.2)	39.3 (0.2)	3.3 (0.1)	53.5 (0.4)
Average of all m.s. analyses (standard deviation)					4.2 (0.5)	39.7 (0.6)	3.4 (0.2)	52.7 (0.6)

Table 1.19. Continued

Experiment No.: 1.19.8
Substrate: CH_3SO_2Cl
Base: Me_3N
pH': 10.74 ± 0.2

Trace No.	Peak heights in millimeters (±0.5). m/e				Percentage composition obtained			
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	11.0	121.0	7.5	117.0	4.3	47.6	2.0	46.7
2	11.5	117.5	9.0	120.0	4.5	45.9	2.6	46.9
3	12.0	121.0	8.0	123.0	4.6	46.2	2.2	47.0
4	11.0	113.5	8.5	115.0	4.5	46.2	2.6	46.8
Average composition					4.5	46.5	2.3	46.7
(standard deviation)					(0.1)	(0.8)	(0.3)	(0.4)

Table 1.19. Continued

Experiment No.: 1.19.9
Substrate: $CH_3SO_2\overset{+}{N}Me_3FSO_3^-$
Base: Me_3N
pH': 10.23 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	1.0	6.5	10.5	133.0	0.7	4.3	6.9	88.1
2	1.0	6.5	9.5	125.5	0.7	4.6	6.6	88.1
3	1.0	6.0	10.0	128.5	0.7	4.1	6.8	88.4
4	1.0	7.0	10.0	123.0	0.7	5.0	7.0	87.3
Average composition (standard deviation)					0.7 (0.0)	4.5 (0.4)	6.8 (0.2)	88.0 (0.5)
2nd m.s. analysis (8300 resolution)								
1	0.5	6.5	10.5	117.0	0.4	4.8	7.7	87.1
2	0.5	7.0	10.5	126.0	0.3	4.9	7.2	87.6
3	0.5	6.0	9.0	126.0	0.4	4.2	6.3	89.1
4	0.5	7.0	11.0	132.0	0.3	4.7	7.2	87.8
Average composition (standard deviation)					0.4 (0.0)	4.7 (0.3)	7.1 (0.6)	87.9 (0.9)
3rd m.s. analysis (8300 resolution)								
1	0.3	5.0	9.5	111.0	0.2	4.0	7.5	88.3
2	0.3	5.0	9.0	113.5	0.2	3.9	7.0	88.9
3	0.4	5.5	9.0	115.5	0.3	4.2	6.8	88.6
4	0.4	5.0	9.0	106.0	0.3	4.2	7.4	88.1

cont'd

Table 1.19. Continued

Experiment No. 1.19.9 (continued)

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
Average composition (standard deviation)					0.3 (0.0)	4.1 (0.1)	7.2 (0.3)	88.5 (0.3)
Average for all m.s. analyses (standard deviation)					0.4 (0.0)	4.4 (0.3)	7.0 (0.4)	88.1 (0.5)

Table 1.19. Continued

Experiment No.: 1.19.10
Substrate: $CH_3SO_2\overset{+}{N}Me_3FSO_3^-$
Base: Me_3N
pH': 10.22 ±0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	0.5	2.0	10.0	109.5	0.4	1.6	8.2	89.8
2	0.5	2.5	11.0	115.0	0.4	1.9	8.5	89.2
3	0.5	3.0	12.0	125.5	0.4	2.1	8.5	89.0
4	0.5	4.0	13.0	114.0	0.4	3.0	9.9	86.7
Average composition (standard deviation)					0.4 (0.0)	2.2 (0.6)	8.8 (0.7)	88.7 (1.3)
2nd m.s. analysis (8300 resolution)								
1	1.5	5.5	12.0	131.0	1.0	3.7	7.9	87.4
2	1.5	5.5	14.0	153.0	0.9	3.2	8.0	88.0
3	1.5	5.0	12.0	142.0	0.9	3.1	7.4	88.5
4	1.5	5.5	8.0	134.0	1.0	3.7	5.3	90.0
5	1.0	4.0	11.0	124.0	0.7	2.9	7.8	88.6
Average composition (standard deviation)					0.9 (0.1)	3.3 (0.4)	7.3 (1.1)	88.5 (1.0)
Average of all m.s. analyses (standard deviation)					0.6 (0.1)	2.7 (0.5)	8.0 (1.0)	88.6 (1.2)

Table 1.19. Continued

Experiment No.: 1.19.11
Substrate: CH_3SO_2Cl
Base: Me_3N
pH': 10.25 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (9100 resolution)								
1	21.5	116.5	6.5	112.0	8.5	45.8	1.7	44.1
2	19.0	107.0	6.0	97.5	8.4	47.0	1.7	42.9
3	19.5	100.0	5.5	88.5	9.2	47.2	1.7	41.9
4	17.5	87.0	4.5	78.0	9.5	46.9	1.5	42.1
Average composition					8.9	46.7	7.6	42.7
(standard deviation)					(0.5)	(0.6)	(0.1)	(1.0)

Table 1.19. Continued.

Experiment No.: 1.19.12
Substrate: CH_3SO_2Cl
Base: Me_3N
pH': 10.24 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	23.0	126.0	7.0	108.0	8.8	48.1	1.7	41.3
2	21.0	118.0	6.5	106.0	8.4	47.3	1.7	42.6
3	18.0	110.0	5.5	99.0	8.2	47.7	1.4	42.7
4	22.0	115.0	6.0	109.0	8.8	46.0	1.5	43.7
Average composition					8.5	47.3	1.6	42.6
(standard deviation)					(0.3)	(0.9)	(0.1)	(1.0)

Table 1.19. Continued

Experiment No.: 1.19.13
Substrate: $CH_3SO_2\overset{+}{N}EtMe_2FSO_3^-$
Base: $EtNMe_2$
pH: 10.73 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	2.0	10.5	19.5	125.0	1.3	6.7	12.3	79.7
2	2.0	10.0	20.5	130.0	1.2	6.2	12.5	80.1
3	2.5	10.0	20.5	133.5	1.5	6.0	12.2	80.2
4	2.0	10.0	19.5	125.0	1.3	6.4	12.4	79.9
Average composition (standard deviation)					1.3 (0.1)	6.3 (0.3)	12.4 (0.1)	80.0 (0.2)
2nd m.s. analysis (8000 resolution)								
1	0.5	5.5	19.5	133.5	0.3	3.5	12.2	84.0
2	0.5	5.5	17.0	121.5	0.3	3.8	11.7	84.1
3	0.4	5.5	19.5	117.5	0.4	3.9	13.6	82.2
4	0.5	5.5	17.5	105.5	0.4	4.3	13.5	81.8
Average composition (standard deviation)					0.4 (0.4)	3.8 (0.4)	12.8 (0.9)	83.0 (1.2)

cont'd

Table 1.19. Continued

Experiment No.: 1.19.13 (cont'd)

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
3rd m.s. analysis (8000 resolution)								
1	0.5	5.5	19.0	127.5	0.3	3.6	12.4	83.6
2	0.5	5.0	19.5	131.0	0.3	3.2	12.5	84.0
3	0.5	5.0	17.5	121.0	0.3	3.5	12.1	84.0
4	0.5	6.0	19.0	120.0	0.3	4.1	13.0	82.5
5	1.0	5.0	19.0	128.0	0.7	3.3	12.4	83.7
Average composition (standard deviation)					0.4 (0.1)	3.5 (0.4)	12.5 (0.3)	83.6 (0.6)
Average of all m.s. analyses (standard deviation)					0.7 (0.7)	4.6 (0.7)	12.5 (0.6)	82.2 (0.9)

Table 1.19. Continued

Experiment No.: 1.19.14
Substrate: $CH_3SO_2\overset{+}{N}EtMe_2FSO_3^-$
Base: $EtNMe_2$
pH': 10.74 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8000 resolution)								
1	0.5	4.5	17.0	110.5	0.4	3.4	12.8	83.4
2	0.5	5.5	16.0	108.5	0.4	4.2	12.2	83.2
3	0.5	4.5	17.5	114.0	0.4	3.3	12.8	83.5
4	0.5	6.5	20.0	121.0	0.3	4.4	13.6	81.8
5	0.5	6.0	17.0	117.5	0.4	4.3	12.0	83.4
Average composition					0.4	3.9	12.7	83.0
(standard deviation)					(0.0)	(0.5)	(0.6)	(0.7)
2nd m.s. analysis (8000 resolution)								
1	0.5	4.0	16.5	103.0	0.4	3.2	13.3	83.1
2	0.5	4.5	17.0	107.0	0.4	3.5	13.2	83.0
3	0.5	5.0	17.5	115.0	0.4	3.6	12.7	83.4
4	0.5	4.0	17.5	108.5	0.4	3.1	13.4	83.1
Average composition					0.4	3.4	13.1	83.1
(standard deviation)					(0.0)	(0.3)	(0.3)	(0.2)
Average of all m.s.					0.4	3.6	12.9	83.1
(standard deviation)					(0.0)	(0.4)	(0.5)	(0.6)

Table 1.19 continued

Experiment No.: 1.19.T5
Substrate: CH_3SO_2Cl
Base: $EtNMe_2$
pH': 10.75 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	3.0	135.5	13.0	126.0	1.1	49.3	3.8	45.8
2	2.0	136.0	16.0	133.0	0.7	47.9	4.7	46.7
3	2.0	140.0	13.0	125.0	0.7	50.5	3.7	45.0
4	2.5	130.0	14.5	124.0	0.9	48.5	4.5	46.1
5	2.5	132.5	11.5	122.0	0.9	49.9	3.3	45.8
Average composition					0.9	49.2	4.0	45.9
(standard deviation)					(0.2)	(1.1)	(0.6)	(0.6)

Table 1.19. Continued

Experiment No.: 1.19.16
Substrate: CH_3SO_2Cl
Base: $EtNMe_2$
pH': 10.74 ± 0.2

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	79	80	91	20	D_0	D_1	D_2	D_3
1st m.s. analysis (8300 resolution)								
1	2.0	144.5	16.5	134.0	0.7	49.2	4.6	45.5
2	2.0	150.0	13.5	130.0	0.7	51.3	3.6	44.4
3	3.5	145.0	13.0	124.5	1.2	51.2	3.6	43.9
4	2.5	143.0	11.0	118.5	0.9	52.6	3.0	43.5
Average composition (standard deviation)					0.9 (0.3)	51.1 (1.4)	3.7 (0.7)	44.3 (0.9)
2nd m.s. analysis (8000 resolution)								
1	1.5	125.5	14.0	100.5	0.6	52.6	4.8	42.0
2	2.0	105.0	11.5	88.0	1.0	51.4	4.6	43.0
3	3.0	124.0	13.0	114.0	1.2	49.3	4.2	45.3
4	5.0	132.0	11.5	117.0	1.9	50.2	3.4	44.5
5	4.0	112.0	13.0	110.0	1.7	47.3	4.6	46.4
Average composition (standard deviation)					1.3 (0.5)	50.2 (2.0)	4.3 (0.6)	44.2 (1.8)
Average for all m.s. analysis (standard deviation)					1.1 (0.4)	50.6 (1.8)	4.0 (0.6)	44.3 (1.4)

Table 1.19. Continued

Experiment No.: 1.19.17
Substrate: CH_3SO_2Cl
Base: $EtNMe_2$
pH': 10.76 ± 0.2

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_2
1st m.s. analysis (8300 resolution)								
1	2.0	145.0	14.5	119.0	0.7	52.3	4.2	42.8
2	2.5	143.5	16.5	112.0	0.9	52.9	5.0	41.2
3	2.5	131.0	12.0	108.0	1.0	52.2	3.8	43.0
4	2.0	134.5	15.5	112.0	0.8	51.5	4.9	42.8
5	2.0	138.0	14.0	107.0	0.8	53.5	4.4	41.4
Average composition (standard deviation)					0.8 (0.1)	52.5 (0.7)	4.5 (0.5)	42.2 (0.9)
2nd m.s. analysis (8700 resolution)								
1	2.0	110.0	10.0	110.0	0.9	47.9	3.4	47.8
2	2.5	109.0	14.5	92.0	1.2	50.6	5.7	42.6
3	2.5	113.0	14.0	94.0	1.1	51.1	5.3	42.9
4	3.0	120.0	16.0	109.0	1.2	48.9	5.6	44.3
Average composition (standard deviation)					1.1 (0.2)	49.6 (1.5)	5.0 (1.1)	44.3 (2.5)

cont'd.

Table 1.19. Continued

Experiment No.: 1.19.17 (Cont'd)

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
3rd m.s. analysis (8300 resolution)								
1	2.5	139.0	18.5	131.0	0.9	48.3	5.5	45.4
2	3.5	129.0	20.0	123.0	1.3	47.3	6.4	45.0
3	3.0	132.5	16.5	131.0	1.1	47.3	5.0	46.7
4	2.5	122.0	18.0	125.0	0.9	46.1	5.9	47.1
Average composition (standard deviation)					1.0 (0.2)	47.2 (0.9)	5.7 (0.6)	46.0 (1.0)
Average of all m.s. analyses (standard deviation)					1.0 (0.2)	49.8 (1.1)	5.0 (0.7)	44.2 (1.5)

Table 1.19. Continued

Experiment No.: 1.19.18
Substrate: $CH_3SO_2NEt_2MeFSO_3^-$
Base: Et_2NMe
pH': 10.79 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (2000 resolution)								
1	5.5	66.0	64.0	134.0	2.1	25.0	23.7	49.2
2	5.0	64.0	63.5	135.0	1.9	24.4	23.7	50.0
3	5.5	65.0	64.0	136.0	2.1	24.5	23.6	49.8
4	5.5	64.0	64.0	133.5	2.1	24.5	23.9	49.5
Average composition					2.0	24.6	23.7	49.6
(standard deviation)					(0.1)	(0.3)	(0.1)	(0.3)

Table 1.19: Continued

Experiment No.: 1.19.19
Substrate: $CH_3SO_2\overset{+}{N}Et_2MeFSO_3^-$
Base: Et_2NMe
pH': 10.74

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (2000 resolution)								
1	5.5	81.0	66.0	140.0	1.9	28.3	22.5	47.2
2	5.5	80.5	69.0	142.0	1.9	27.7	23.2	47.2
3	5.0	82.5	66.5	140.5	1.7	28.7	22.5	47.1
4	5.5	80.0	69.0	136.0	1.9	28.2	23.7	46.2
5	6.0	80.0	63.0	137.0	2.2	28.6	21.9	47.3
Average composition					1.9	28.3	22.8	47.0
(standard deviation)					(0.1)	(0.4)	(0.7)	(0.5)

Table 1.19. Continued

Experiment No.: 1.19.20
Substrate: $CH_3SO_2\overset{+}{N}Et_2MeFSO_3^-$
Base: Et_2NMe
pH': 10.73 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (2000 resolution)								
1	5.5	87.0	68.0	144.0	1.9	29.3	22.2	46.6
2	5.5	86.0	68.0	143.5	1.9	29.1	22.3	46.7
3	5.5	81.5	64.0	139.0	1.9	28.8	22.0	47.3
4	5.0	81.5	62.5	137.0	1.8	29.2	21.7	47.3
5	5.0	84.5	65.5	143.0	1.7	29.0	21.9	47.4
Average composition (standard deviation)					1.8 (0.1)	29.1 (0.2)	22.0 (0.3)	47.1 (0.3)
2nd m.s. analysis (standard deviation)								
1	5.0	79.0	67.0	124.0	1.9	29.4	24.3	44.4
2	6.0	79.0	66.0	130.0	2.2	28.8	23.4	45.6
3	5.5	81.0	65.0	129.5	2.0	29.5	23.1	45.4
4	6.0	76.0	66.0	131.0	2.2	27.9	23.6	46.3
5	6.0	78.0	63.0	128.0	2.2	29.1	22.8	45.9
Average composition (standard deviation)					2.1 (0.1)	28.9 (0.6)	23.4 (0.6)	45.5 (0.7)
Average of all m.s. analyses (standard deviation)					2.0 (0.1)	29.0 (0.5)	23.7 (0.5)	46.3 (0.6)

Table 1.19. Continued

Experiment No.: 1.19.21
Substrate: CH_3SO_2Cl
Base: Et_2NMe
pH': 10.77 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (10,000 resolution)								
1	3.5	110.5	19.0	27.5	2.2	69.9	10.7	17.2
2	3.0	110.0	22.0	24.5	1.9	70.1	12.6	15.4
3	4.5	141.0	26.0	31.0	2.3	70.8	11.7	15.3
4	4.0	145.0	28.0	33.0	1.9	70.2	12.2	15.7
Average composition (standard deviation)					2.1 (0.2)	70.2 (0.4)	11.8 (0.9)	15.9 (0.9)

Table 1.19.

Experiment No.: 1.19.22
Substrate: CH_3SO_2Cl
Base: Et_2NMe
pH': 10.76 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (2000 resolution)								
1	2.5	141.5	24.5	30.0	1.3	75.1	11.5	12.1
2	2.5	142.0	24.5	29.5	1.3	75.4	11.5	11.8
3	2.5	137.0	23.5	29.5	1.4	75.0	11.3	12.3
4	2.5	136.0	23.5	29.0	1.4	75.0	11.4	12.2
Average composition (standard deviation)					1.4 (0.0)	75.1 (0.2)	11.4 (0.1)	12.1 (0.2)
2nd m.s. analysis (2000 resolution)								
1	2.5	141.0	24.0	29.0	1.3	75.6	11.3	11.7
2	2.0	138.0	23.5	28.5	1.1	76.0	11.3	11.6
3	2.0	133.0	22.5	27.0	1.1	76.0	11.3	11.6
4	2.0	131.5	22.5	27.0	1.2	75.7	11.4	11.7
5	2.0	130.0	21.5	27.0	1.2	75.9	11.0	11.9
Average composition (standard deviation)					1.2 (0.1)	75.8 (0.1)	11.3 (0.2)	11.7 (0.1)

cont'd

Table 1.19. Continued

Experiment 1.19.22. (cont'd)

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
3rd m.s. analysis (8000 resolution)								
1	2.0	149.0	24.0	30.0	1.0	73.9	10.4	14.7
2	2.5	138.0	23.5	28.0	1.3	73.1	11.0	14.6
3	2.5	135.0	22.5	27.0	1.4	73.4	10.8	14.5
4	2.5	135.5	22.5	28.0	1.3	73.1	10.7	14.9
Average composition (standard deviation)					1.3 (0.2)	73.4 (0.4)	10.7 (0.3)	14.7 (0.2)
Average of all m.s. analyses (standard deviation)					1.3 (0.3)	74.8 (0.3)	11.1 (0.2)	12.8 (0.2)

Table 1.19. Continued

Experiment No.: 1.19.23
Substrate: CH_3SO_2Cl
Base: Et_2NMe
pH': 10.73 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (2,000 resolution)								
1	2.5	134.0	18.5	24.5	1.5	78.8	9.3	10.4
2	2.0	130.5	18.0	23.5	1.2	79.2	8.3	10.3
3	2.0	129.0	17.5	23.5	1.2	79.2	9.1	10.4
4	2.0	129.0	18.0	22.5	1.2	79.4	9.5	9.9
5	2.0	128.5	17.0	22.5	1.2	79.9	8.9	10.0
Average composition (standard deviation)					1.3 (0.1)	79.3 (0.4)	9.2 (0.2)	10.2 (0.3)
2nd m.s. analysis (8300 resolution)								
1	2.5	123.0	14.5	21.5	1.6	77.4	7.6	13.4
2	3.0	117.0	13.5	20.0	2.0	77.5	7.4	13.1
3	2.5	112.0	14.0	18.0	1.7	77.7	8.2	12.3
4	2.5	131.0	16.5	21.0	1.5	77.9	8.3	12.3
5	2.0	128.0	17.0	21.0	1.2	77.4	8.8	12.5
Average composition (standard deviation)					1.6 (0.3)	77.6 (0.2)	8.1 (0.5)	12.7 (0.5)

cont'd

Table 1.19. Continued

Experiment No.: 1.19.23 (cont'd)

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
3rd m.s. analysis (8000 resolution)								
1	2.0	124.0	17.5	27.5	1.2	73.7	8.9	16.2
2	2.0	138.5	19.5	27.5	1.1	75.1	9.1	14.7
3	2.0	137.5	19.5	29.0	1.1	74.3	9.1	15.5
4	3.5	140.0	19.5	32.0	1.8	72.9	8.7	16.5
Average composition (standard deviation)					1.3 (0.4)	74.0 (0.9)	9.0 (0.2)	15.7 (0.8)
Average of all m.s. analyses (standard deviation)					1.4 (0.3)	76.8 (0.6)	8.7 (0.6)	12.9 (0.5)

Table 1.19. Continued

Experiment No.: 1.19.24
Substrate: CH_3SO_2Cl
Base: Et_2NMe
pH': 10.72 ± 0.02

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st m.s. analysis (10,000 resolution)								
1	2.0	136.0	21.5	33.0	1.1	71.8	9.9	17.2
2	1.5	127.0	21.0	28.0	0.9	72.7	10.6	15.8
3	2.0	140.5	23.5	28.0	1.0	73.6	10.9	14.5
4	2.0	132.0	20.5	26.0	1.1	74.3	10.1	14.4
Average composition (standard deviation)					1.0 (0.1)	73.1 (1.1)	10.4 (0.4)	15.5 (1.3)
2nd m.s. analysis (8000 resolution)								
1	1.5	114.0	21.0	26.0	0.9	71.3	11.7	16.0
2	2.0	110.0	19.5	26.0	1.3	71.0	11.2	16.6
3	1.5	106.5	19.0	26.0	1.0	70.7	11.2	17.0
4	2.0	117.5	19.5	29.0	1.2	71.1	10.4	17.3
5	1.5	101.0	16.0	25.0	1.1	71.5	9.9	17.5
Average composition (standard deviation)					1.1 (0.1)	71.1 (0.3)	10.9 (0.7)	16.9 (0.6)

cont'd

Table 1.19. Cont'd

Experiment No.: 1.19.24. (cont'd)

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
3rd m.s. analysis (8000 resolution)								
1	2.5	125.0	22.0	38.5	1.4	67.5	10.6	20.6
2	2.0	138.5	23.0	37.0	1.0	70.2	10.3	18.5
3	2.5	140.0	26.5	41.0	1.2	67.7	11.5	19.6
4	2.0	151.5	29.0	45.0	0.9	67.6	11.6	19.9
Average composition (standard deviation)					1.1 (0.2)	68.3 (1.3)	11.0 (0.7)	19.6 (0.8)
Average of all m.s. analysis (standard deviation)					1.1 (0.2)	70.8 (0.9)	10.8 (0.6)	11.3 (0.9)

Table 1.20. Average Results Obtained from the Multiexchange Experiments to Six Significant Figures as Used in Computer Simulations (Program FINDK)

Base Used	pH'	Percentage Compositions: Trialkyl(methylsulfonyl)ammonium fluorosulfate				Methanesulfonyl Chloride			
		D_0	D_1	D_2	D_3	D_0	D_1	D_2	D_3
Me_3N	10.7	1.10551	1.40155	11.5517	85.9413	3.91740	44.3779	2.95126	48.7535
Me_3N	10.2	0.543000	3.56960	7.53566	88.3517	8.73107	46.9875	1.61357	42.6680
$EtNMe_2$	10.7	0.533941	4.10150	12.7204	82.6441	0.983545	49.9812	4.35102	44.7942
Et_2NMe	10.7	1.97573	22.2225	23.3301	47.4717	1.45372	73.1988	10.6043	14.7431

In order to determine the reproducibility of the mass spectral measurement selected samples were resubmitted once or twice at time intervals varying from 1 day to 6 weeks. In the case of reanalyzed samples the average composition for all the analyses are presented in the table after the results of the last analysis of a particular sample. The calculations, unless otherwise noted, were performed using the programs MS79PL for low resolution and MS79PH for high resolution measurements. These programs are discussed in Appendix 3. Table 1.20 contains the average results to six significant figures for the experiments reported in Table 1.19. These were used in the computing (program FINDK) to avoid errors that may have arisen due to repeated round-off during program execution.

The Reaction of Methanesulfonyl Chloride with Triethylamine in the Multiexchange Medium Prepared Using Water and Deuterium Oxide

The reaction medium was prepared in the manner outlined for multiexchange except that a mixture of water (37.73 mL) and deuterium oxide (40.90 mL) was used in place of pure deuterium oxide so that the ratio of active hydrogen to deuterium was 0.9225 and triethylamine (4.04 g, 40 mmol) was used as the amine base. The pH' of the reaction was 10.75 ± 0.02. The sulfonyl chloride (0.31 mL, 4.0 mmol) in acetonitrile (10 mL) was added as previously described. Workup and mass spectral analysis gave the results shown in Table 1.21.

Table 1.21. Product Distribution Obtained from the Reaction of Methanesulfonyl Chloride with Triethylamine in the Multiexchange Medium Prepared Using Water and Deuterium Oxide.

Trace No.	Peak heights in millimeters (±0.5)				Percentage Composition Obtained[a]			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st ms analysis (2000 resolution)								
1	147.5	84.5	7.5	4.0	64.4	35.6	0.0	0.0
2	148.0	84.0	7.5	4.0	64.6	35.4	0.0	0.0
3	146.0	84.0	8.0	4.0	64.3	35.7	0.0	0.0
4	146.5	84.5	7.5	4.0	64.6	35.4	0.0	0.0
Average composition (standard deviation)					64.5 (0.2)	35.5 (0.2)	0.0 -	0.0 -

a: calculations performed by hand using the correction factors C_1 = 1.988%, C_2 = 4.8% and C_3 = 0.048% as described in the text.

The Reaction of Methanesulfonyl Chloride with Triethylamine in the Multiexchange Medium

The reaction medium was prepared in the manner outlined for multiexchange except that triethylamine (4.04 g, 40 mmol) was used. The pH' for the reaction was 10.77 ± 0.02. The sulfonyl chloride (0.31 mL, 4.0 mmol) in acetonitrile (10 mL) was added as previously described. Workup and mass spectral analysis gave the results shown in Table 1.22.

Aqueous Quenching of the Multiexchange Reaction of Methanesulfonyl Chloride with Trimethylamine

The quenching solution was prepared by adding trimethylamine (34.8 mL at -20°C, 400 mmol) to a solution of hydrochloric acid (390 mL, 0.42 M), acetonitrile (50 mL) and dimethoxyethane (35 mL).

The multiexchange solution was prepared as described in the general method. The pH' was 10.75 ± 0.02. The solution was transferred to a 1 L plastic beaker and stirred vigorously with a 5 cm magnetic stirring bar and the pH' remeasured (10.72 ± 0.02). The sulfonyl chloride was added as described in the general method. This was immediately followed by the addition of the quenching solution. The addition time for the quench was appoximately 10 s. The workup followed that of the general procedure except that after the organic solvents and free trimethylamine were removed by pumping down the reaction solution at ~0.1 torr the addition of excess hydrochloric acid was used to destroy the excess carbonate. The solution was then evaporated to dryness and baked at 120°C for 4 h to ensure that traces of water were removed.

Table 1.22. Product Distribution Obtained from the Reaction of Methanesulfonyl Chloride with Triethylamine in the Multiexchange Medium.

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st ms analysis (2000 resolution)								
1	2.5	141.0	4.0	7.0	1.7	97.4	0.8	0.2
2	2.5	140.0	4.0	7.0	1.7	97.3	0.8	0.2
3	2.5	139.0	4.0	7.0	1.7	97.2	0.8	0.2
4	2.5	138.0	4.0	7.0	1.8	97.2	0.8	0.3
5	2.5	139.0	4.0	7.0	1.7	97.2	0.8	0.2
Average composition (standard deviation)					1.7 (0.0)	97.3 (0.1)	0.8 (0.0)	0.1 (0.0)

before the addition of phosphorous pentachloride. The sulfonyl chloride was obtained in the usual manner and subjected to mass spectral analysis to determine the product distribution shown in Table 1.23.

Aqueous Quenching of the Multiexchange Reaction of Trimethyl(methylsulfonyl)ammonium Fluorosulfate

The procedure for the quenching of the methanesulfonyl chloride multiexchange reaction was followed. The pH' was 10.75 before addition of the quench and 10.55 after addition of the quench. Workup and mass spectral analysis gave the results reported in Table 1.24.

The Determination of pK_a' of Potassium Carbonate and the Tertiary Amines

The following tables (1.25 to 1.29) present the results of the titration of potassium carbonate and the four tertiary amines, trimethyl, dimethylethyl, methyldiethyl and triethylamine in the solvent system used for the multiexchange reactions. The conditions and apparatus used were those of the multiexchange reactions except that the titrant (6.09 M DCl) was delivered via an automatic syringe. For the titrations of the amines potassium chloride (1.00 g, 13.4 mmol) was added to compensate for the absence of the potassium carbonate on the ionic strength based on the assumption that at the pH' used for the multiexchange experiments the carbonate anion is approximately half neutralized. The pK_a' were determined graphically using the half neutralization point of the base.

Table 1.23. Product Distribution Obtained from Aqueous Quenching of the Reaction of Methanesulfonyl Chloride with Trimethylamine.

Trace No.	Peak heights in millimeters (±0.5)				Percentage compositions obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st ms analysis (8000 resolution)								
1	42.0	130.5	7.0	70.0	17.1	52.7	1.8	28.4
2	43.0	127.0	7.0	65.0	18.0	52.9	1.9	27.2
3	39.0	127.0	6.0	70.0	16.3	52.9	1.5	29.3
4	36.0	116.0	6.0	62.0	16.6	53.1	1.7	28.5
5	39.0	114.0	5.0	60.5	18.1	52.6	1.3	28.1
Average composition (standard deviation)					17.2 (0.8)	52.8 (0.3)	1.6 (0.3)	28.3 (0.8)

Table 1.24. Product Distribution Obtained from Aqueous Quenching of the Reaction of Trimethyl(methylsulfonyl)ammonium Fluorosulfate.

Trace No.	Peak heights in millimeters (±0.5)				Percentage composition obtained			
	m/e							
	79	80	81	82	D_0	D_1	D_2	D_3
1st ms analysis (8000 resolution)								
1	33.0	93.0	40.5	300.0	7.1	19.9	8.3	64.6
2	33.0	81.0	34.0	220.0	9.0	22.0	8.9	60.1
3	36.5	87.0	36.5	330.0	7.5	17.7	7.1	67.6
4	39.5	93.0	38.0	315.0	8.2	19.1	7.5	65.2
Average composition (standard deviation)					8.0 (0.8)	19.7 (1.8)	8.0 (0.8)	64.4 (3.2)

Table 1.25. Results Obtained from the Titration of Potassium Carbonate.

Amount Base: 0.827 mg, 5.98 mmol
Medium: deuterium oxide (15.7 mL)
acetonitrile (2.0 mL)
dimethoxyethane (1.4 mL)
Titrant: deuterium chloride in deuterium oxide (6.09 M)
pKa' determined: 10.53 ± 0.02.

Volume DCl in millilitres	pH (meter reading) ±0.02	Volume DCl in millimeters	pH (meter reading) ±0.02
0.0000	12.36	0.3192	10.87
0.0107	12.19	0.3349	10.84
0.0198	12.07	0.3456	10.82
0.0223	12.04	0.3632	10.78
0.0257	12.00	0.3801	10.75
0.0324	11.93	0.4030	10.71
0.0399	11.85	0.4202	10.68
0.0495	11.79	0.4345	10.65
0.0538	11.76	0.4585	10.61
0.0602	11.72	0.4741	10.58
0.0658	11.68	0.4950	10.53
0.0734	11.64	0.5247	10.49
0.0803	11.60	0.5664	10.41
0.0877	11.56	0.6141	10.32
0.0913	11.54	0.6548	10.24
0.0967	11.52	0.6960	10.15
0.1018	11.49	0.7236	10.07
0.1063	11.47	0.7537	10.00
0.1129	11.45	0.7907	9.89
0.1204	11.42	0.8099	9.84
0.1247	11.40	0.8635	9.76
0.1296	11.38	0.8911	9.52
0.1344	11.36	0.9119	9.39
0.1421	11.34	0.9411	9.14
0.1469	11.31	0.9578	8.90
0.1524	11.30	0.9687	8.70
0.1593	11.28	0.9828	8.39
0.1666	11.26	0.9984	8.09
0.1743	11.24	1.0237	7.77
0.1834	11.21	1.0423	7.63
0.1919	11.18	1.0607	7.52
0.1984	11.15	1.0838	7.41
0.2117	11.11	1.1082	7.32
0.2246	11.08	1.1394	7.24
0.2403	11.04	1.1605	7.20*
0.2548	11.01	1.1746	7.22
0.2647	10.99	1.2608	7.11
0.2790	10.96		
0.2938	10.92		
0.3040	10.90		

* evolution of carbon dioxide begins

Table 1.26. Titration Data for Trimethylamine

Amount Base: 0.35 mL at -17 C 4.0 mmol
Solvents: deuterium oxide (15.7 mL)
acetonitrile (2.0 mL)
dimethoxyethane (1.4 mL)
potassium chloride (1.0 g)
Titrant: deuterium chloride in deuterium oxide (6.09 M)
pK_a' determined: 10.31 (±0.02)

Volume DCl in millilitres	pH (meter reading) ±0.02	Volume DCl in millimeters	pH (meter reading) ±0.02
0.0000	12.08	0.3050	10.32
0.0184	12.77	0.3199	10.28
0.0317	11.57	0.3335	10.24
0.0412	11.46	0.3474	10.21
0.0502	11.37	0.3607	10.16
0.0597	11.29	0.3731	10.13
0.0673	11.24	0.3853	10.09
0.0756	11.18	0.3980	10.05
0.0840	11.13	0.4134	9.99
0.0933	11.08	0.4259	9.95
0.1033	11.02	0.4321	9.91
0.1143	10.95	0.4531	9.85
0.1248	10.91	0.4659	9.81
0.1383	10.85	0.4809	9.75
0.1511	10.80	0.4965	9.68
0.1644	10.75	0.5116	9.60
0.1774	10.71	0.5255	9.53
0.1909	10.66	0.5422	9.42
0.2043	10.62	0.5588	9.30
0.2177	10.58	0.5728	9.16
0.2330	10.53	0.5845	8.98
0.2468	10.49	0.5986	8.65
0.2629	10.44	0.6112	7.55
0.2766	10.40	0.6245	2.16
0.2920	10.36		

Table 1.27. Titration Data for Dimethylethylamine.

Amount Base: 296 mg, 4.04 mmol
Medium: deuterium oxide (15.7 mL)
acetonitrile (2.0 mL)
dimethoxyethane (1.4 mL)
potassium chloride (1.0 g)
Titrant: deuterium chloride in deuterium oxide (6.09 M)
pK'_a determined: 10.50 (±0.02)

Volume DCl in millilitres	pH (meter reading) ±0.02	Volume DCl in millilitres	pH (meter reading)
0.0000	12.25	0.3500	10.42
0.0162	11.94	0.3664	10.38
0.0279	11.90	0.3859	10.33
0.0420	11.79	0.4020	10.28
0.0540	11.65	0.4238	10.22
0.0658	11.54	0.4405	10.16
0.0801	11.43	0.4552	10.12
0.0951	11.33	0.4760	10.05
0.1085	11.26	0.4922	9.97
0.1233	11.18	0.5119	9.89
0.1362	11.12	0.5314	9.80
0.1482	11.07	0.5476	9.72
0.1645	10.99	0.5582	9.66
0.1764	10.94	0.5758	9.54
0.1864	10.90	0.5916	9.39
0.2051	10.85	0.6080	9.18
0.2208	10.79	0.6179	8.95
0.2382	10.74	0.6282	8.47
0.2546	10.69	0.6362	3.65
0.2682	10.65	0.6440	2.49
0.2845	10.61		
0.2987	10.57		
0.3158	10.52		
0.3343	10.47		

Table 1.28. Titration Data for Diethylmethylamine.

Amount Base: 351 mg, 4.02 mmol.
Medium: deuterium oxide (15.7 mL)
acetonitrile (2.0 mL)
dimethoxyethane (1.4 mL)
Potassium chloride (1.4 g)
Titrant: deuterium chloride in deuterium oxide (5.09 M)
pK_a' determined: 10.76 (±0.02)

Volume DCl in millilitres	pH' (±0.02)	Volume DCl in millilitres	pH' (±0.02)
0.0000	12.37	0.2804	10.84
0.0135	12.15	0.2951	10.80
0.0284	11.99	0.3091	10.77
0.0472	11.81	0.3223	10.73
0.0568	11.74	0.3397	10.69
0.0671	11.67	0.3557	10.64
0.0754	11.61	0.3711	10.60
0.0875	11.54	0.3858	10.56
0.0983	11.49	0.4002	10.52
0.1103	11.43	0.4147	10.48
0.1217	11.38	0.4293	10.43
0.1322	11.33	0.4449	10.38
0.1479	11.27	0.4643	10.32
0.1589	11.23	0.4838	10.25
0.1708	11.19	0.5006	10.18
0.1818	11.15	0.5156	10.12
0.1948	11.11	0.5349	10.02
0.2055	11.08	0.5542	9.89
0.2138	11.03	0.5685	9.79
0.2244	11.00	0.5814	9.67
0.2382	10.96	0.5963	9.48
0.2504	10.93	0.6132	9.07
0.2647	10.89	0.6267	3.50

Table 1.29. Titration Data for Triethylamine.

Amount Base: 4.04 mg, 4.00 mmol
Medium: deuterium oxide (15.7 mL)
acetonitrile (2.0 mL)
dimethoxyethane (1.4 mL)
potassium chloride (1.0 g)
Titrant: deuterium chloride in deuterium oxide (6.09 M)
pK_a' determined: 11.18 (±0.02)

Volume DCl in millilitres	pH (meter reading) ±0.02	Volume DCl in milliliters	pH (meter reading) ±0.02
0.0000	12.59	0.2917	11.25
0.0215	12.39	0.3059	11.21
0.0328	12.29	0.3204	11.17
0.0431	12.20	0.3343	11.13
0.0529	12.13	0.3552	11.08
0.0657	12.05	0.3706	11.02
0.0770	11.98	0.3877	10.97
0.0890	11.92	0.4070	10.91
0.1006	11.87	0.4212	10.87
0.1108	11.82	0.4391	10.81
0.1242	11.77	0.4569	10.75
0.1342	11.73	0.4719	10.70
0.1440	11.69	0.4890	10.64
0.1557	11.65	0.5029	10.58
0.1676	11.61	0.5160	10.52
0.1773	11.58	0.5322	10.44
0.1890	11.54	0.5485	10.35
0.2018	11.50	0.5644	10.24
0.2167	11.46	0.5854	10.05
0.2301	11.42	0.5976	9.87
0.2463	11.37	0.6098	9.64
0.2604	11.33	0.6231	8.98
0.2753	11.29		

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CHAPTER 2

NUCLEOPHILIC CATALYSIS IN THE REACTION OF METHANESULFONYL CHLORIDES WITH TERTIARY AMINES IN ORGANIC SOLVENT

2.1 Introduction

In the introduction to Chapter 1 it was pointed out that incorporation of one and only one deuterium in the product of the reaction of a tertiary amine with an aliphatic sulfonyl chloride in the presence of a deuterium labelled trap indicated that sulfene had been formed. King and Durst (1) found that the use of a large excess of trap (typically twenty-fold) gave products which were usually greater than 90% monodeuterated (see Table 1.1) with the remainder of the product being nondeuterated. Truce and Campbell (2), using only a very small excess of trap (typically 1.2 fold) obtained a much lower proportion of monodeuterated product (45-50%), the remainder being the nondeuterated product. Neither group saw any sign of perdeuterated product with the relatively bulky bases used. As has been discussed in the previous chapter the use of small bases (eg. trimethylamine) does result in the formation of perdeuterated product from the reaction in deuterium oxide.

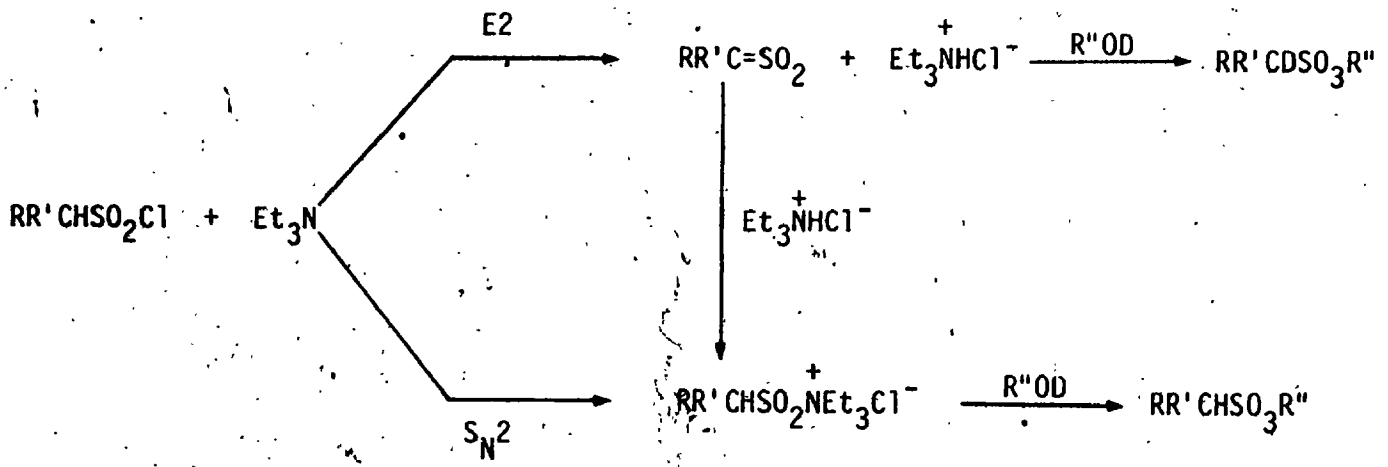
The incorporation of only one deuterium in the product was taken by both groups as good evidence for sulfene formation but the interpretation of the formation of the nondeuterated product differed. King and Durst proposed that the nondeuterated material results from a combination of a number of possible factors; a small but significant amount of a direct displacement mechanism, dilution of the isotopic purity of the trap with the isotope removed from the sulfonyl chloride, a kinetic isotope effect in the trapping of sulfene, and a higher local concentration of the isotope abstracted from the sulfonyl chloride by the amine due to slow diffusion of the ammonium ion so formed relative to sulfene trapping. Truce and Campbell proposed that the nondeuterated

product was the result of nucleophilic attack by the amine on the sulfonyl group to form an intermediate followed by a second nucleophilic attack by the trap to form product, the first step of this direct displacement mechanism having precedent in reactions of aromatic sulfonyl chlorides (3).

From the reaction of methanesulfonyl chloride with triethylamine in the presence of methanol-d Truce and Campbell obtained 20-45% yields of methyl mesylate. The isotopic compositions of these products has been summarized in Table 1.2. The general procedure used was to add slowly a solution of the sulfonyl chloride in benzene to a solution of triethylamine and methanol-d in the same solvent at room temperature under a nitrogen atmosphere. After stirring for 1.5 h the trimethylammonium chloride formed was removed by filtration. The benzene filtrate was dried and the solvent removed by evaporation. Distillation at reduced pressure gave the product.

The results obtained were rationalized using the mechanistic scheme shown in Figure 2.1. As mentioned earlier, in this scheme formation of nondeuterated product is via two nucleophilic displacements (by base followed by alcohol). This pathway was termed the S_N2 route and the elimination to form sulfene followed by trapping by alcohol the E2 route. These two competing reaction pathways were proposed since the authors assumed that the alcohol trap remained fully deuterated on oxygen throughout the course of the reaction. This necessitates that the amine hydrochloride produced during sulfene formation precipitates from solution before it has the opportunity either to donate a proton in the trapping of sulfene or to exchange the deuterium of the trap for a proton. Two control experiments were cited to support the above

Figure 2.1. Mechanistic Scheme proposed by Truce and Campbell for the Reaction of Triethylamine with Aliphatic Sulfonyl Chlorides[a].



a: from reference 19.

assumption:

1. Triethylammonium chloride was stirred as a suspension in a benzene solution of methanol-d and triethylamine for 1 h. The triethylammonium chloride was recovered and found not to contain deuterium as measured by infrared spectroscopy.

2. The normal trapping experiment was performed using unlabelled methanol. After one hour methanol-d was added and stirring continued for 30 minutes. The recovered ammonium salt was examined for deuterium incorporation as above. None was detected.

Neither of these two controls examines the possibility that the ammonium salt can act as a proton source immediately after its formation but before sufficient aggregation has taken place for crystals to form and precipitate the salt from solution thereby sequestering the hydrogen from further exchange.

The authors also found an increase in the amount of monodeuterated product formed with an increase in the amount of deuterated trap used. This increase was rationalized by proposing a competition between sulfene trapping by methanol-d and triethylammonium chloride (see Figure 2.1). Thus with more trap present the reaction of sulfene with methanol-d would be more favored.

Truce and Campbell are thus suggesting that the triethylammonium chloride is capable of reacting with the sulfene to give the sulfonylammonium salt before it precipitates but not of exchanging hydrogens with methanol-d. When one notes that the most characteristic - and rapid - reactions of sulfenes are those with nucleophilic reagents

(which the triethylammonium cation is not) and that the transfer of hydrogen ions between amines and alcohols is rapid (4,5), the Truce and Campbell scheme must be regarded as highly suspect. The observation of multiexchange by Luinstra (6) and Harding (7) however, does point to the involvement of sulfonylammonium salts at least with "small" or "unhindered" tertiary amines, and these results especially when taken with du Manoir's experiments with sulfonylammonium salts, indicate that the reaction of tertiary amines with methanesulfonyl chloride in the presence of alcohols should be reinvestigated to determine the role, if any, of sulfonylammonium salts.

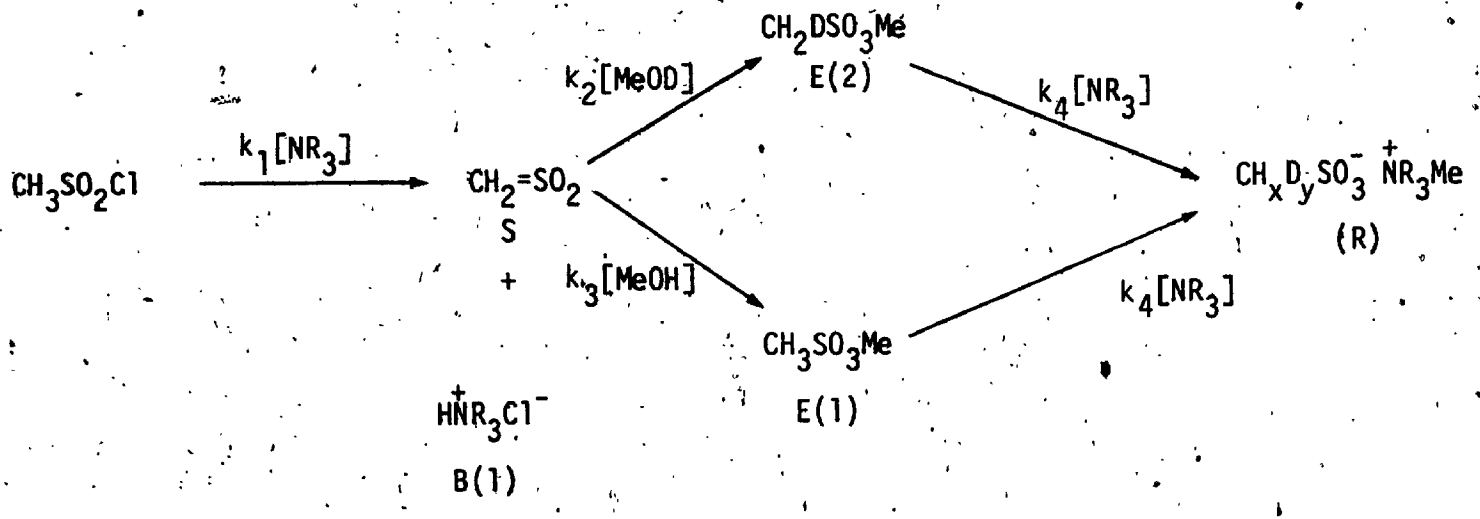
Since the scheme proposed by Truce and Campbell would appear to have deficiencies and has been used by other workers (8,9) to rationalize their own results, a discussion of what is believed to be a simpler alternative will be presented in the next section of this chapter. This is followed by a description and discussion of experiments designed to assess the possibility of nucleophilic catalysis in sulfene formation in a non-aqueous medium.

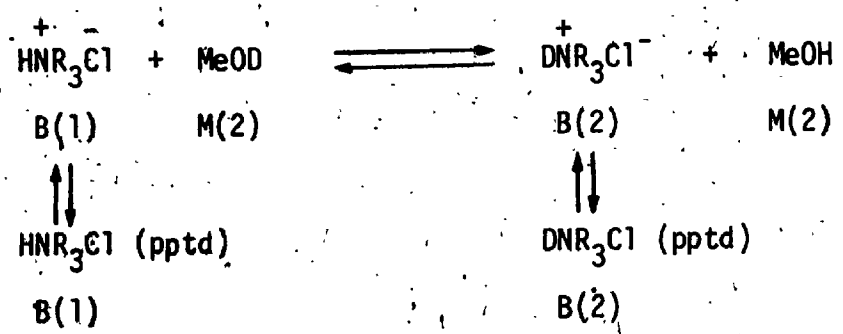
2.2 Results and Discussion

Figure 2.2 shows a mechanism which is proposed to accommodate the results obtained by Truce and Campbell for the reaction of methanesulfonyl chloride with triethylamine in benzene when only a moderate excess of trap is used. This mechanism does not include the formation of a triethyl(methylsulfonyl)ammonium salt in any way. The suggested mechanism specifically includes the exchange of a proton for deuterium between $Et_3\overset{+}{N}H$ and the trap, methanol-d, to form the base deuterochloride

Figure 2.2.

Reaction Scheme for the Base Catalysed Reaction of Methanesulfonyl Chloride with Methanol-d in Organic Solvent[a]





a: The symbols used in SIMTR4 appear below each species.

and ordinary methanol, leading to dilution of the isotopic purity of the trap.

That the mechanistic scheme shown in Figure 2.2 can easily accommodate the results of Truce and Campbell was demonstrated by a number of computer simulations, the results of which are summarized in Table 2.1. The program used to simulate this scheme is described in Appendix 4.

A discussion of the experimental error was not provided by Truce and Campbell who used nmr integration to determine the extent of deuteration on the product esters. The results, which appear in the discussion of the extent of nucleophilic catalysis in the second half of this section, shown in Table 2.2 for the reaction of diethylmethylamine with methanesulfonyl chloride do give an indication of the error which can be expected. The results shown in entries 4 and 5 of this table give values of 59 and 45% for the percent monodeuteration in the product. Thus any model which produces monodeuteration in the range of 45-60%, for example, would appear to accommodate the results. In developing the model for computer simulation the following assignments and assumptions were used:

1. The sulfonyl chloride concentration was called C, the free base N, the sulfene S, methanol M(1), methanol-d M(2), the nondeuterated ester E(1), the deuterated ester E(2) the methylated amine R, the amine hydrochloride B(1) and the amine deuterochloride B(2).
2. The initial concentration of methanesulfonyl chloride was set at 1.0. The initial concentrations of free base and methanol-d were then assigned the appropriate relative values.

Table 2.1

Summary of Results Obtained from Computer

Simulation of the Mechanism of Figure 2.2.

Entry No.	Mechanistic Variant	Initial Concentrations C	N	M(a)	Relative Rate Constants k_1	k_2	k_3	k_4	Product Concentrations[a] E(1)	E(2)	R	E(2)/(E(1)+E(2))
1	A	1	1.3	1.2	1.0	100	200	0.0	0	0.97	0.0	1.0
2	B	1	1.3	1.2	1.0	100	200	1.0	0.14	0.18	0.49	0.56
3	B	1	1.3	4.0	1.0	100	200	1.0	0.06	0.26	0.49	0.80
4	C	1	1.3	1.2	1.0	100	200	0.0	0.49	0.48	0.03	0.50
5	C	1	1.3	1.2	1.0	100	200	0.01	0.47	0.48	0.03	0.50
6	C	1	1.3	1.2	1.0	100	200	0.1	0.38	0.37	0.21	0.50
7	C	1	1.3	1.2	1.0	100	200	0.5	0.23	0.23	0.41	0.50
8	C	1	1.3	1.2	1.0	100	200	1.0	0.16	0.15	0.49	0.48
9	C	1	1.3	1.2	1.0	100	200	2.0	0.10	0.09	0.55	0.46
10	C	1	1.3	1.2	1.0	100	200	5.0	0.05	0.03	0.61	0.41
11	C	1	1.3	4.0	1.0	100	200	1.0	0.07	0.25	0.49	0.79
12	C	1	1.3	20.0	1.0	100	200	1.0	0.02	0.30	0.49	0.95
13	C	1	1.3	1.2	1.0	10	20	1.0	0.17	0.16	0.48	0.47
14	C	1.0	1.3	1.2	1.0	200	400	1.0	0.16	0.15	0.49	0.47
15	C	1.0	1.3	1.2	1.0	100	170	1.0	0.16	0.16	0.49	0.50
16	C	1.0	1.3	1.2	1.0	100	225	1.0	0.17	0.15	0.49	0.47
17	C	1.0	1.3	1.2	1.0	100	100	1.0	0.14	0.18	0.49	0.57
18	C	1.0	1.3	1.2	1.0	100	400	1.0	0.19	0.13	0.49	0.39
19	C	1.0	1.3	1.2	1.0	100	700	1.0	0.21	0.10	0.49	0.33
20	D	1.0	1.3	1.2	1.0	100	200	1.0	0.14	0.18	0.49	0.56
21	E	1.0	1.3	1.2	1.0	100	200	1.0	0.16	0.15	0.49	0.48

a: since the formation of methyltriethylammonium mesylate (R) requires two moles of amine the total amount of products does not always equal the amount of methanesulfonyl chloride used. However all the simulations reported were run to greater then 96% completion based on either the sulfonyl chloride (C) or the amine (N).

3. The rate constant for the formation of sulfene from sulfonyl chloride and amine (k_1) was assigned a value of 1.0.
4. The rate constant for sulfene trapping with methanol-d (k_2) was set at 100 since sulfene trapping is fast relative to sulfene generation. As long as the value of k_2 used was large with respect to k_1 the choice of a value for k_2 did not affect the results in a significant manner. This may be seen by comparing entries 8, 13 and 14 of Table 2.1.
5. The rate constant for trapping of sulfene with methanol (k_3) was assigned from the value for k_2 taken with Kang's (10) value of 2.0 for the kinetic isotope effect for trapping of phenylsulfene with isopropyl alcohol. Kang's value was an average of two measurements (1.7 and 2.25). These two values were also used, along with isotope effects of 1, 4 and 7 to assess the sensitivity of the predicted results to the choice of kinetic isotope effect in the sulfene trapping reaction. Examination of the results presented in entries 15-19 with the results of entry 8 indicate that the isotope effect would have to be greater than 4 in order for the predicted results to be appreciably different from those predicted using Kang's value of 2.0.
6. The rate constant (k_4) for alkylation of free base by the product esters was assigned a value of 1.0 so that the final "yield" of the esters would be about 32% which is midway in range of yields (20 to 45%) obtained by Truce and Campbell. Variation of k_4 (see entries 4-10) does not result in a significant change in the proportion of deuterated ester

obtained, even when k_4 is such that simulation predicts a lower amount (entry 10) or higher amounts (entries 4-6) of product esters than found experimentally.

The computer program (SIMTR4) was used to estimate the product composition from five variations of the mechanism shown in Figure 2.2. These were:

A. The base hydrochloride formed during the elimination of hydrogen chloride from methanesulfonyl chloride precipitates from solution before it can react with any other species in solution (ie. the original assumption of Truce and Campbell)

B. The base hydrochloride dilutes the deuterium content of the solution before the sulfene generated during its formation is trapped, and remains in solution until the reaction is complete.

C. The base hydrochloride generated during sulfene formation dilutes the deuterium content of the solution before the sulfene generated during its formation is trapped, and then precipitates.

D. The base hydrochloride generated during sulfene formation dilutes the deuterium content of the solution after the sulfene generated during its formation is trapped and remains in solution until the reaction is complete.

E. As in D but the base hydrochloride (deuterium enriched) precipitates from solution.

Variations B and D were expected to become equivalent as the time interval (see Appendix 4) used for simulation becomes zero. Similarly,

variations C and E were expected to become equivalent. These expectations were borne out as shown by the results in entries 2 vs. 20 and 8 vs. 21. As a result only the differences between A, B (or D), and C (or E) have to be considered.

Variations B and C differ in that B assumes that the base hydrochloride is in solution for the whole reaction; ie. homogeneous conditions. In C the base hydrochloride precipitates immediately after it has diluted the isotopic purity of the reagents. Variation B is the situation which was found to be occurring during the trapping experiments carried out in methylene chloride solution by King and Durst. Truce and Campbell on the other hand, who use benzene as the solvent, reported the appearance of a precipitate during their experiments but did not report whether the precipitate appeared during the addition of the substrate to the reagent or afterward. Since sulfene generation and trapping are relatively fast processes the timing of the precipitation of the base hydrochloride, whether it occurs after all the sulfene has been generated and trapped (variation B), shortly after base hydrochloride formation (variation C), or somewhere in between, cannot be determined. As a result a comparison of the simulations for the limiting cases (B and C) will be made but the possibility that the actual situation may be somewhere between the two must be noted.

Entry 1 of Table 2.1 gives the results from the computer simulation of variation A of the mechanism of Figure 2.2 in which the base hydrochloride precipitates from solution before it can dilute the deuterium content of the trap, ie. the Truce and Campbell proposal. As expected the predicted ratio of the deuterium labelled product to the total product was one, ie. the product was 100% monodeuterated.

The results for the simulations of variation B are listed in entries 2 and 3. Entry 2 shows that when the base hydrochloride is allowed to remain in solution to dilute the label of the trap there is a dramatic decrease in the percentage of the monodeutered product to deuterated product (56% with 1.2 equivalents of methanol-d). When 4.0 equivalents were used the percentage was 80% (entry 3). As mentioned previously these two simulations would correspond to the experiments of King and Durst if they had used lower amounts of trap.

The simulated results for variation C are shown in entries 3 to 19. Most of these simulations were done to determine the effect of varying the input parameters for the program and have been discussed previously. For variation C the key entries are 8, 11 and 12 which present the simulated results for 1.2, 4.0 and 20.0 equivalents of methanol-d. The calculated percentages of deuterated product were 48, 79 and 95.

The experimental result obtained by Truce and Campbell for the reaction of methanesulfonyl chloride with triethylamine and 1.2 equivalents of methanol-d in benzene was a 48% deuteration of the product. From results with diethylmethylamine (see above) the true value is expected to be between 40 and 56%. Both of the simulations shown in entries 2 and 8 predict deuterations in this range; 56% for variation B and 46% for variation C. The result for variation A (100% deuteration) is outside of this range. Therefore the simulations indicate that a mechanism which allows the hydrogen abstracted from the starting material to appear in the product can explain the experimental results quantitatively.

This idea that the hydrogen of the starting material can appear in the product, has recently been confirmed by preliminary results

by Skonieczny (11). From the reaction of a mixture of phenylmethanesulfonyl chloride-α-d_2 and methanesulfonyl chloride with triethylamine in benzene, Skonieczny was able to isolate a significant amount of deuterium labelled methanesulfonate. This proves experimentally, contrary to Truce and Campbell's assumption, that the hydrogen abstracted from a sulfonyl chloride can appear in the product.

The previous discussion shows that the basis on which Truce and Campbell proposed that a methylsulfonylammonium salt is formed during the reaction of triethylamine with methanesulfonyl chloride is incorrect and that their results can be accounted for without invoking such an intermediate. It is still possible, however, that this salt is being formed during the reaction. By subjecting triethyl(methylsulfonyl)ammonium chloride to the reaction conditions of Truce and Campbell one could expect to learn about the extent of its formation during the reaction of methanesulfonyl chloride with triethylamine by comparing the product compositions. Since this salt is not available and du Manoir (12) was not able to obtain product from the methylation of more hindered sulfonamides such as the N,N-diisopropyl, N,N-dibutyl and N-methyl-N-phenyl methanesulfonamides, diethylmethyl(methylsulfonyl)ammonium fluorosulfate was used to carry out an investigation of the possible role of such a salt in the reaction of an aliphatic sulfonyl chloride with amine bases, in particular to investigate the amount of nucleophilic catalysis.

The general procedure used by Truce and Campbell was adapted so that the diethylmethyl fluorosulfonate salt could be added to the benzene solution of base and alcohol while maintaining a homogeneous system. Instead of using 3 mL of benzene to deliver the salt (or the sulfonyl chloride) 3 mL of anhydrous acetonitrile was used. In order to show

that this change in the solvent system does not give significantly different results Truce and Campbell's experiments were repeated under their conditions as well as those of this study as described in the experimental section of this chapter.

The results obtained are listed in Tables 2.2 and 2.3. Entries 1 through 5 of Table 2.2 show that the results obtained with diethylmethylamine are similar to those of triethylamine. The use of the less hindered amine does result in a reduction in yield. This is probably due to the more facile alkylation of diethylmethylamine by methyl methanesulfonate. Entries 6 and 7 give the results obtained using 4 equivalents and 20 equivalents of trap to sulfonyl chloride respectively, the latter experiment not having been reported by Truce and Campbell. Entries 8, 9, and 10 show that the benzene-acetonitrile solvent system gives results comparable to the pure benzene solvent system. Table 2.3 summarizes the results obtained with diethyl(methylsulfonyl)ammonium fluorosulfate.

It is evident from the data in Tables 2.2 and 2.3 (compare for example entry 10 in Table 2.2 with entry 4 in Table 2.3) and especially from the labelling patterns shown in Figures 2.3 and 2.4 that the reactions of methanesulfonyl chloride and diethylmethyl(methylsulfonyl) ammonium fluorosulfate with diethylmethylamine give quite different isotopic distribution patterns. This result immediately excludes all mechanisms in which $k_2' >> k_1$ (Scheme 2.1). One may go even further and try, as was done in Chapter 1, to estimate the maximum proportion of $MeSO_2Cl$ that is converted into $MeSO_2\overset{+}{N}Et_2Me$ in the reaction with Et_2NMe. Making the conservative estimate from the spectra shown in

Table 2.2.

Results Obtained from the Reaction of Methanesulfonyl Chloride[a] with Tertiary Amines and Methanol-d in Organic Solvents

Entry No.	Amine	mmol MeOD	Solvent(s) (mL)	Atoms D in product[b] (yield in percent)
1	Et_3N	12.0	benzene[c] (13.0)	0.47[d] (25)[e]
2	Et_3N	12.0	dry benzene[f] (13.0)	0.59 (33)
3	$MeEt_2N$	12.0	benzene (13.0)	0.45 (12)
4	$MeEt_2N$	12.0	dry benzene (13.0)	0.59 (14)
5	$MeEt_2N$	12.0	dry benzene (13.0)	0.45 (10)
6	$MeEt_2N$	40.0	dry benzene (13.0)	0.76 (26)
7	$MeEt_2N$	200.0	dry benzene (13.0)	0.90 (41)
8	Et_3N	12.0	dry benzene:acetonitrile[g] (10.0:3.0)	0.56 (38)

.../2

Table 2.2. (continued)

Entry No.	Amine	mmol MeOD	Solvent(s) (mL)	Atoms D in product[b] (yield in percent)
9	$MeEt_2N$	12.0	dry benzene:acetonitrile (10.0:3.0)	0.68 (17)
10	$MeEt_2N$	200.0	dry benzene:acetonitrile (10.0:3.0)	1.06[h] (44)

a: 10 mmol of methanesulfonyl chloride and 13 mmol of tertiary amine base were used

b: the 1:2:3:2:1 signal characteristic of CD_2H was not observed in the ^1H nmr spectra using an XL100 nmr spectrometer.

c: reagent grade benzene

d: determined by comparing the integral of the methylsulfonyl peak to that of the methyl ester peak

e: yield obtained after solvent removal by evaporation

f: reagent grade benzene dried by distillation from calcium hydride

g: distilled from phosphorus pentoxide

h: 0.978 atoms D by combustion analysis. ^{13}C spectrum shown in Figure 2.3.

Table 2.3.

Results Obtained from the Reaction of Diethylmethyl(methylsulfonyl)-ammonium fluorosulfonate[a] in Benzene: Acetonitrile (10.0:3.0)[b] with Diethylmethylamine and Methanol-d.

Entry No.	mmol Amine	mmol MeOD	Atoms D in product[c] (yield in percent)
1	1.0	200.0	1.71[d] (74)[e]
2	3.0	12.0	0.47 (34)
3	3.0	40.0	0.84 (33)
4	3.0	200.0	1.27[f] (41)
5	3.0	200.0	1.21 (26)
6	3.0	200.0	1.43 (43)
7	8.0	200.0	0.97 (32)
8	8.0	200.0	0.94 (25)
9	8.0	200.0	1.09[g] (29)
10	20.0	200.0	0.61 (9)
11	30.0	200.0	0.83
12	30.0	200.0	0.81 (16)

a: 10.0 mmol

b: 10.0 ml benzene dried by distillation from calcium hydride and 3.0 ml acetonitrile dried by distillation from phosophorus pentoxide

c: the 1:2:3:2:1 signal characteristic of CD_2H was observed in the ^1H nmr spectra using a XL-100 nmr spectrometer

d: determined by comparing the integral of the methylsulfonyl peak to that of the methyl ester peak.

e: yield obtained after solvent removed by evaporation

f: 1.17 atoms D by combustion analysis; ^{13}C nmr spectrum shown in Figure 2.5.

g: 0.858 atoms D by combustion analysis; ^{13}C nmr spectrum shown in Figure 2.4.

Figure 2.3. ^{13}C nmr Spectrum of the Product of the Reaction of Methanesulfonyl Chloride with 20.0 Equivalents of Methanol-d and 1.3 Equivalents of Diethylmethylamine in Benzene: Acetonitrile

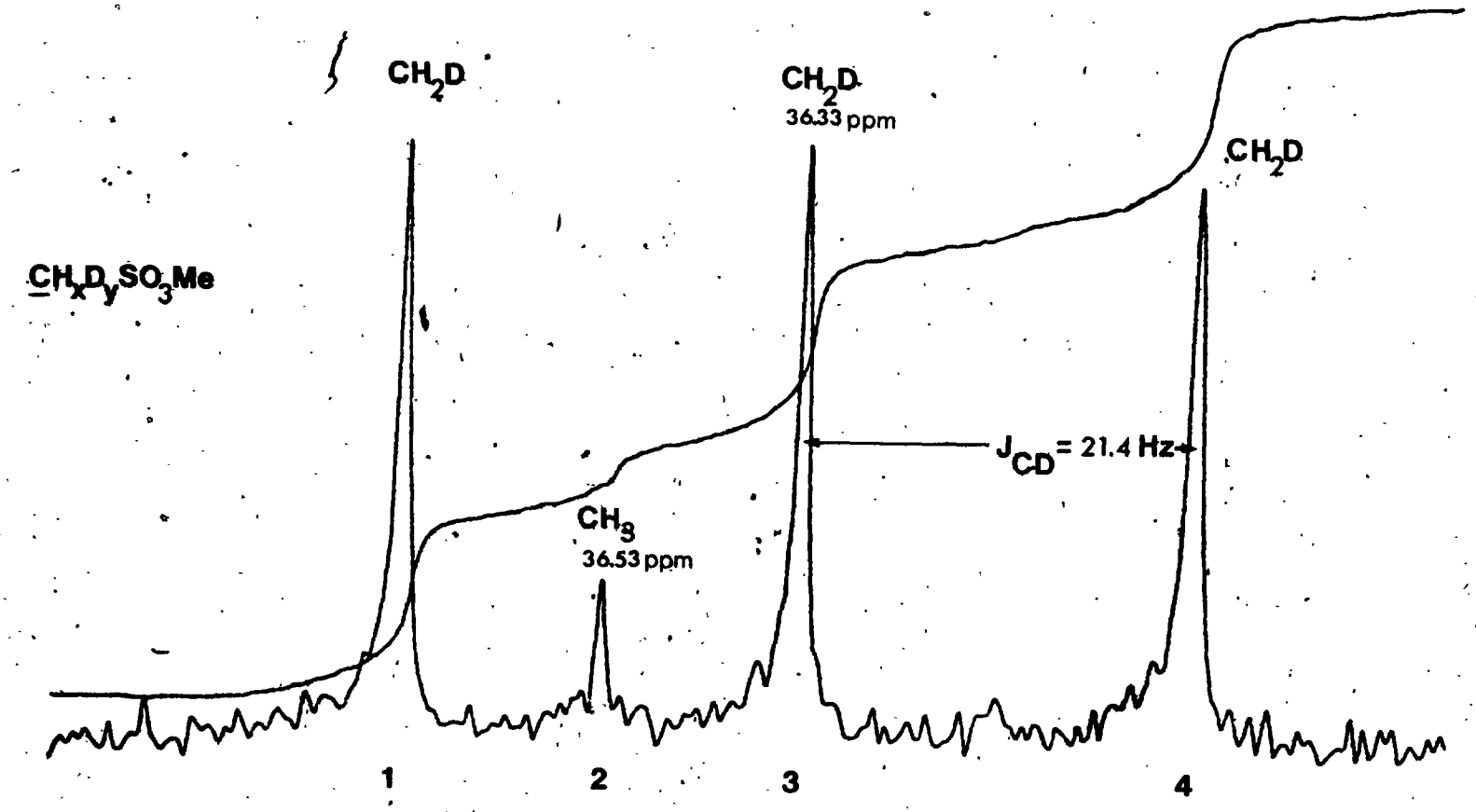
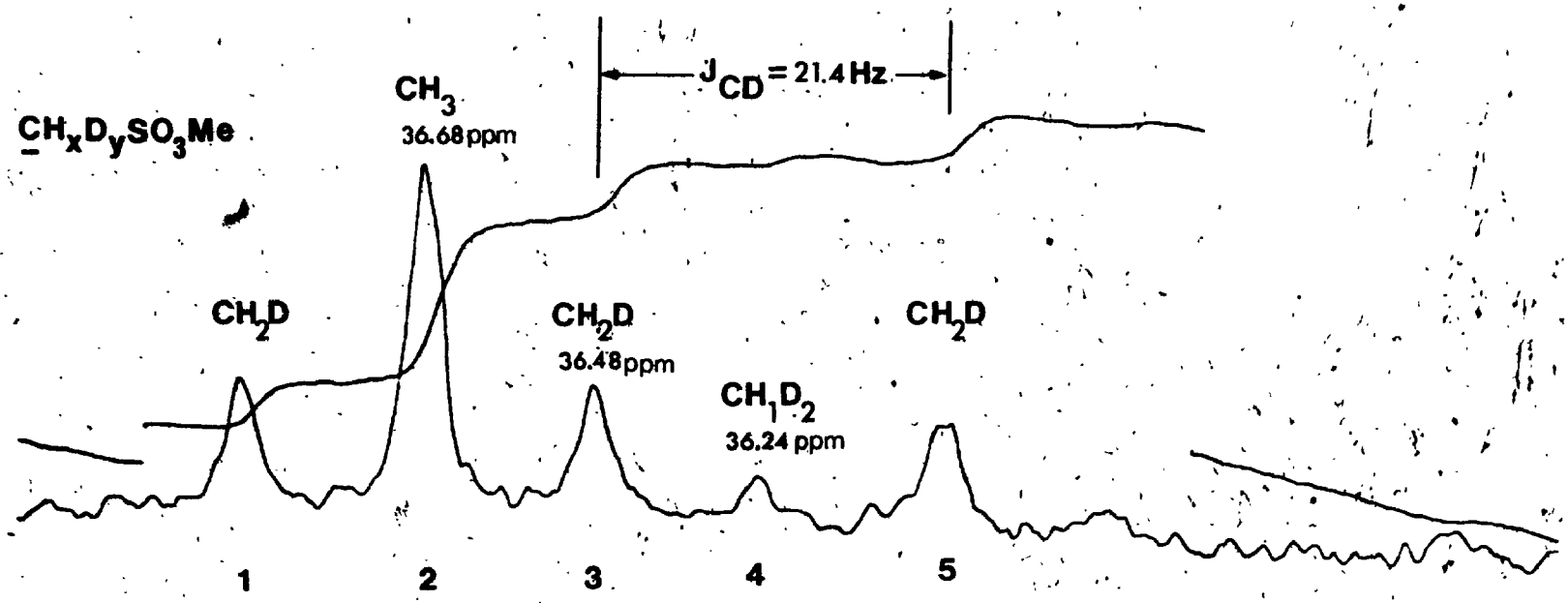
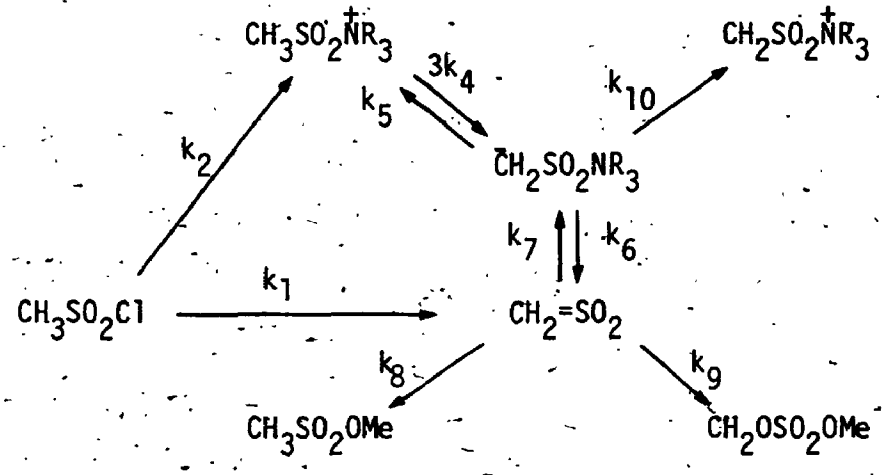


Figure 2.4. ^{13}C nmr Spectrum of the Product of the Reaction of Diethylmethyl(methylsulfonyl)ammonium Fluorosulfonate with 20.0 Equivalents of Methanol-d and 0.8 Equivalents of Diethylmethylamine in Benzene: Acetonitrile.



Scheme 2.1



Figures 2.3 and 2.4 that we would be able to detect 5% of $CHD_2SO_3^-$ if it were present we may then readily deduce that k_1 must be $\sim k_2$. This follows from the observation that starting with $MeSO_2\overset{+}{N}Et_2MeFSO_3^-$ and 0.8 equivalents of amine a 10% yield of $CHD_2SO_3^-$ was found, and hence a reaction in which 50% of the reaction product arises via $MeSO_2\overset{+}{N}Et_2Me$ (because $k_1/k_2 = 1$) must give 0.50 x 10% = 5% of $CHD_2SO_3^-$ or a quantity that might just escape direct observation by ^{13}C nmr.

It should be noted that while the reaction of methanesulfonyl chloride consumes one equivalent of base, the reaction of diethylmethyl(methylsulfonyl)ammonium fluorosulfate does not. To obtain identical reaction conditions the two sets of reactions should ideally be carried out under conditions in which the amine concentration stays essentially constant. Unfortunately as may be seen in Table 2.3 an increase in the amount of base used decreases the yield of methyl methanesulfonate obtained, presumably because of alkylation of the amine, and it is not feasible to obtain an adequate recovery of the product

under true psuedo-first order conditions. The various concentrations of base used in the experiments of Table 2.3 where chosen to bracket the variation in amine concentration that would occur in the reaction of methanesulfonyl chloride as the amine is consumed. For all of these experiments a signal due to $-CD_2H$ was observed in the proton spectra while the proton spectra of the reactions of methanesulfonyl chloride (Table 2.2) did not show a $-CH_2H$ signal. This clearly indicates that the two starting materials produce different labelling patterns in the products. The products of the reaction of the salt (entry 9 of Table 2.3) with 0.8 equivalents of base were examined by ^{13}C nmr (see Figure 2.4). This was done since 0.8 equivalents of base represents the midway point in the reaction of methanesulfonyl chloride with 1.3 equivalents of base as this reaction would leave 0.3 equivalents of base left over upon complete consumption of the sulfonyl chloride. This assumes that alkylation of base by the product methyl methanesulfonate was slow relative to the main reaction.

The labelling pattern for the reaction of the salt, $MeSO_2\overset{+}{N}Et_2MeFSO_3^-$, for the reaction with 0.3 equivalents of base was also determined. Although the total deuterium content was not determined by combustion analysis, an estimation of its value was made by multiplying the total deuterium content obtained from the XL100 spectrum by 0.877 which is the average correction factor to convert the deuterium content measured by nmr to the values obtained from combustion analysis (see the experimental section). For this experiment the percentage of nondeuterated material drops to 20% while the percentage of dideuterated material becomes 20%, the values for mono- and trideuterated product not changing as appreciably (see the experimental section). The values

for dideuterated product in the two experiments are not very different when one considers the estimated experimental error. However the change in levels of nondeuterated product; 20% with 0.3 equivalents of base and 40% with 0.8 is clearly significant. The origin of this change is not readily apparent. A possible explanation is that while the reaction rates of Scheme 2.1 are fast several of them (eq. k_4) become even faster with 0.8 equivalents of base versus 0.3 equivalents and that this allows even less diffusion of the ammonium ion from the sulfene thereby increasing the likelihood that sulfene is trapped with a proton rather than a deuteron, i.e. k_8 is effectively increased with respect to k_9. Changes of product distribution due to this type of effect have been postulated by King and Durst (1) and by Thea (13). This effect does not however alter the basic conclusion that the methylsulfonylammonium ion and the sulfonyl chloride do not give the same product distributions.

To obtain the maximum proportion of sulfonylammonium ion that could arise in the reaction of methanesulfonyl chloride with triethylamine we take the same approach as was used in Chapter 1. This results in an R value (k_2/k_1) of 0.16 which implies that less than 14% of the reaction proceeds via the nucleophilic catalysis. For the same reasons as discussed in chapter 1 this value should be regarded as a conservative estimate of the maximum amount of nucleophilic catalysis.

2.3 Conclusions

As a result of the work described in this chapter the following conclusions can be drawn:

1. The results of the computer simulations taken together with Skonieczny's observation that the hydrogen abstracted from a sulfonyl chloride can appear in the sulfene trapping product indicate that a straight forward sulfene formation by elimination followed by trapping that includes isotopic dilution of trap most reasonably accommodates the observed results, and that the scheme of Truce and Campbell is invalid.
2. The extent of nucleophilic catalysis in the reaction of methanesulfonyl chloride with triethylamine is estimated to be less than 14%.

2.4 Experimental

Proton nuclear magnetic resonance (nmr) spectra were recorded on a Varian XL100 spectrometer with tetramethylsilane (TMS) as an internal standard. Carbon nmr were run on a Varian XL200.

Solvents were obtained from Fisher Scientific. Benzene was dried by distillation from calcium hydride. Acetonitrile was dried by distillation from anhydrous phosphorus pentoxide. Triethylamine and methanesulfonyl chloride were obtained from Eastman Chemicals. Methanesulfonyl chloride was redistilled and stored in a dessicator. Diethylmethylamine was obtained from Aldrich Chemicals. Methanol-d was obtained from Merck, Sharp and Dohme Montreal, minimum isotopic

purity 99%. The diethylmethyl(methylsulfonyl)ammonium fluorosulfate was prepared by the method of du Manoir (12).

Deuterium analyses were performed by J. Nemeth of Urbana, Illinois, U.S.A.

General Procedure for the Reaction of Methanesulfonyl Chloride or Diethylmethyl(methylsulfonyl)ammonium fluorosulfonate with Tertiary Amines in the Presence of Methanol-d in Organic Solvents

The general procedure of Truce and Campbell (2) was used on a one tenth scale. Methanesulfonyl chloride (10 mmol) was dissolved in 3 mL solvent and added over 20 minutes to a solution of the amine and methanol-d, in benzene (10 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred 70 minutes. The evolution of heat was observed during the reaction.

The precipitate formed was removed by filtration. The filtrate washed with water, dried and the solvent removed by evaporation at reduced pressure to give methyl methanesulfonate. This material was analyzed for deuterium by comparing the methyl ester signal with that of the methylsulfonyl signal on a XL100 nmr spectrometer. The presence of multiexchanged product was checked by expansion of the methylsulfonyl signal to detect the 1:2:3:2:1 quintet of a $-CD_2H$ group.

The results obtained for methanesulfonyl chloride are summarized in Table 2.2.

The same procedure was used for the reaction with diethylmethyl-(methylsulfonyl) ammonium fluorosulfonate and the results are summarized in Table 2.3.

Calculation of the Labelling Patterns of the Methyl Methanesulfonate Samples using ^{13}C Spectroscopy and Deuterium Combustion Analysis

The ^{13}C spectra for the methylsulfonyl absorption of the methyl methanesulfonate samples obtained from the reaction of methanesulfonyl chloride and from two reactions of diethylmethyl(methylsulfonyl)ammonium fluorosulfate with diethylmethylamine and 20 equivalents of base are shown in Figures 2.3 and 2.4 in the results and discussion section of this chapter and Figure 2.5 of this section.

For the sample of ester obtained from the reaction of methanesulfonyl chloride combustion analysis indicated that there were 0.978 atoms of deuterium in the molecule. From the spectrum shown in Figure 2.3 the relative areas of the peaks were:

Peak Number	1	2	3	4
Relative Area	39	9	40	37

Peak 2 is the $-^{13}CH_3$ signal and peaks 1, 3 and 4 comprise the 1:1:1 triplet due to the $-CDH_2$ signal. Assigning a total peak height of zero to the $-CD_2H$ signals and x for the $-CD_3$ group one obtains the following relative amounts:

$-CH_3$	CH_2D	CHD_2	CD_3
9	115	0	x

Using 0.978 for the total number of deuterium atoms one obtains the relationship:

$$\frac{9(0) + 115(1) + 0(2) + x(3)}{115 + x} = 0.978$$

where the numbers in brackets correspond to the number of deuterium atoms for each of the four types of methyl groups. Solution of this equation gives x = 3. Therefore the relative amounts of each are:

$-CH_3$	$-CH_2D$	$-CHD_2$	CD_3
7	91	0	2
(10±5%)	(90±5%)	(0±5%)	(0±15%)

with the values in brackets indicating the most reasonable values after considering the accuracy of the nmr integrations of the spectra shown in Figure 2.3. The range for the percentage $-CD_3$ is larger than the others as this value was obtained by assuming that the deuterium not accounted for in the other products was contained in the $-CD_3$ group.

For the reaction of diethylmethyl(methylsulfonyl)ammonium fluorosulfate with 0.8 equivalents of diethylmethyl amine (see entry 9 of Table 2.3) the areas of the peaks from the spectrum of Figure 2.4 are:

1	2	3	4	5
13	43	14	3	13

Most of peak number 2 is the $-^{13}CH_3$ signal (see below), peaks 1, 3 and 5 comprise the $-^{13}CH_2D$ signal, and peak 4 is the center of the 1:2:3:2:1 quintet of the $-^{13}CHD_2$ group which overlaps with the $-^{13}CH_3$ signal. Adjustment of integral for peak 2 for the contribution from the $-^{13}CHD_2$ quintet, summing the integrals for peaks 1, 3 and 5 and assigning an integral of 9 to the $-^{13}CHD_2$ signal gives the following relative intensities:

$-CH_3$	$-CH_2D$	$-CHD_2$
40	41	9

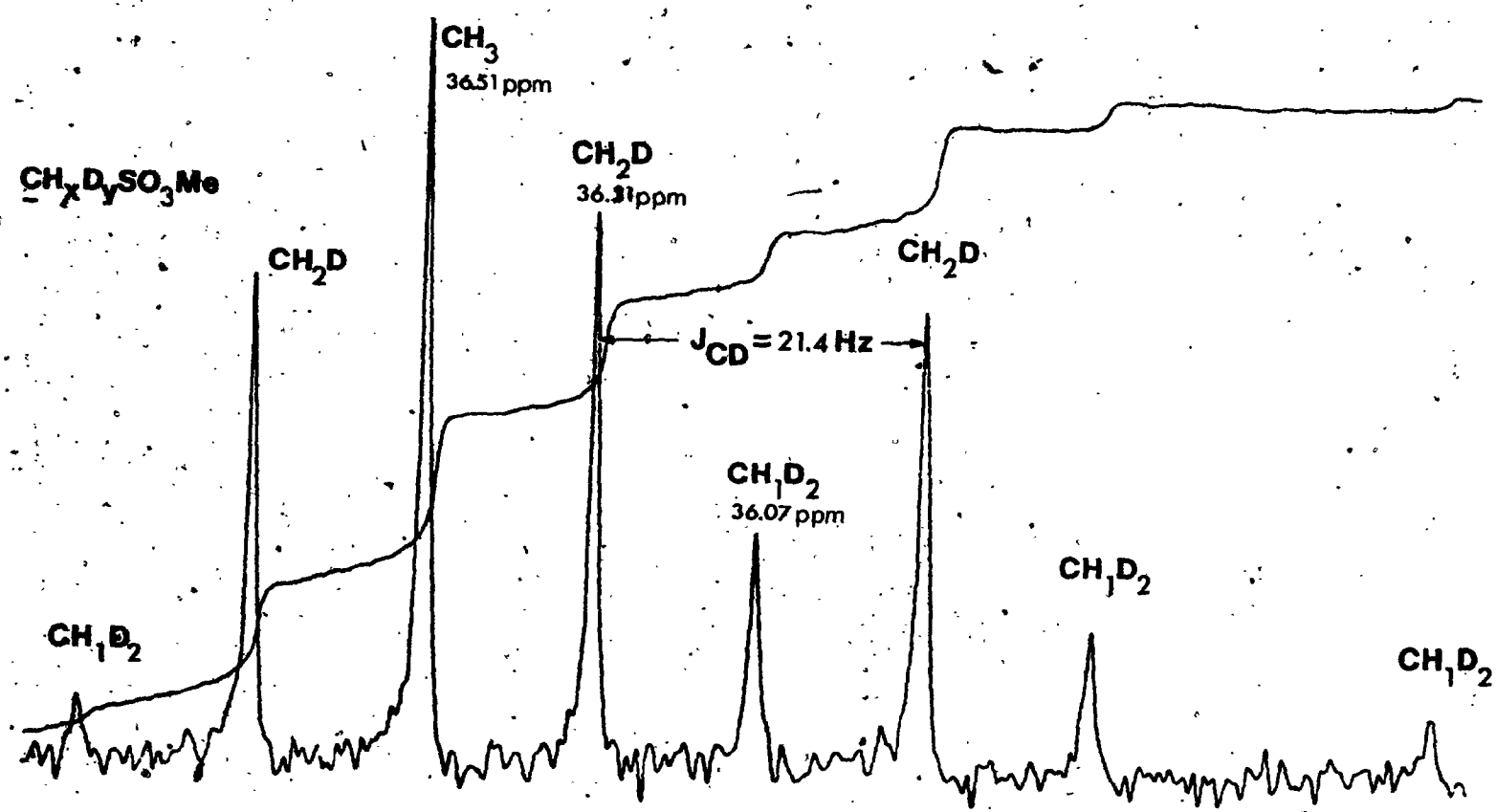
Using the value obtained for the total deuterium content obtained from combustion analysis of 0.858 atoms D/molecule the calculated labelling pattern was:

$-CH_3$	$-CH_2D$	$-CHD_2$	CD_3
42	40	9	9
(40±5%)	(40±5%)	(10±5%)	(10±15%)

For the reaction of the methylsulfonylammonium salt with 0.3 equivalents of base, the ^{13}C nmr spectrum is shown in Figure 2.5. Since a deuterium combustion analysis was not available the total deuterium content was estimated. For entry 10 of Table 2.2 the nmr spectrum indicated a total deuterium content of 0.978 atoms D/molecule while combustion analysis gave a value of 1.06 which results in a "correction factor" of 0.978/1.06 = 0.922 for the nmr value. Similarily the data for entries 4 and 9 produce "correction factors" of 0.921 and 0.787 respectively. The average "correction factor" used to adjust the nmr value of 1.43 atoms D/molecule for entry 6 of Table 2.3 is 0.877 and the estimated total deuterium content becomes 1.25 atoms D/molecule. Using this value and the relative areas from Figure 2.5 the calculated labelling pattern becomes

$-CH_3$	$-CH_2D$	$-CHD_2$	$-CD_3$
(20±5%)	(50±5%)	(20±5%)	(10±15%)

Figure 2.5. ^{13}C nmr Spectrum of the Product of the Reaction of Diethylmethyl-(methylsulfonyl)ammonium Fluorosulfonate with 20.0 Equivalents of Methanol-d and 0.3 Equivalents of Diethylmethylamine in Benzene: Acetonitrile.



2.5 References

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CHAPTER 3

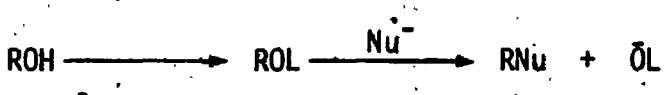
SYNTHESIS AND REACTIONS OF 3-(ALKOXYSULFONYL)-N,N,N,-TRIMETHYLPROPANAMINIUM SALTS (ALKYL [3]BETYLATES) AND 3(ALKOXYSULFONYL)-N,N-DIMETHYLPROPANIMINIUM SALTS (ALKYL [3]NORBETYLATES)

3.1 Introduction

In chapters 1 and 2 sulfonylammonium salts were used to study aspects of sulfene chemistry. The work to be discussed in this chapter also involved a sulfonylammonium ion, but in a synthetic context. Here, a cyclic sulfonylammonium ion (8, in Scheme 3.7) was used to synthesize a member of a new type of leaving group, the ammonioalkanesulfonate esters. These were found to be useful in the conversion of alcohols to a wide variety of derivatives.

The conversion of an alcohol to a product via nucleophilic substitution is a commonly used process in organic chemistry. This conversion usually involves the transformation of the hydroxyl function to a better leaving group (nucleofuge) since hydroxide is a poor leaving group. For the overall process shown in Scheme 3.1 to be useful both steps should proceed in high yield, in a short time, and under experimentally convenient conditions.

Scheme 3.1



Nu: nucleophile

There are a number of difficulties associated with the above approach. These include the low solubility of a nucleophile (eg. cyanide) in the organic solvents often required to dissolve the intermediate, ROL, incomplete reaction within a reasonable time span, the need for high temperatures, difficulties in product workup, poor control of stereochemistry and the occurrence of side reactions.

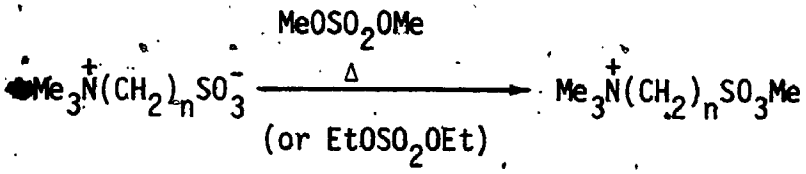
Approaches used to avoid these problems include the use of polar aprotic solvents such as dimethylformamide or hexamethylphosphoramide (1,2) the use of crown ethers (3), phase transfer reagents (4), and more powerful leaving groups (5,6).

Each of these alternatives has advantages and disadvantages with its application to the conversion of an alcohol to a derivative. Polar aprotic solvents have been used successfully in many reactions to ensure that the nucleophile and the substrate are both in solution, thereby accelerating the overall rate of product formation. Unfortunately polar aprotic solvents are often expensive and both difficult to recover and to remove completely from the product, and traces of water may cause side reactions (7). Often elevated reaction temperatures are required (8). The phase transfer catalysis approach avoids many of the drawbacks encountered in the application of polar aprotic solvents. Phase transfer catalysis (PTC) offers experimental convenience, excellent control of reaction temperature, ease of workup and purification along with the frequent absence of side reactions related to solvolysis (9). However the quaternary ammonium salts commonly used in this approach to nucleophilic substitution are not always stable to strong alkali, may be difficult to recover, and occasionally, form emulsions. The use of macrocyclic ethers (crown ethers) to increase the solubility of a salt such as potassium hydroxide in organic solvents also has merit in enabling a charged nucleophile to react with a substrate dissolved in the organic phase. By complexing the cation of the anionic nucleophile the solubility of the salt is increased. This approach allows anhydrous conditions to be maintained during the reaction. In addition crown ethers are

stable (9). Disadvantages to the crown ether approach include relatively high cost, the need to have the right ether for a particular cation, difficulty in removing the crown ether from the product, and the acute toxicity of these ethers. Powerful leaving groups have also found application in nucleophilic substitution. In addition to the more commonly used mesylate and tosylate groups, triflates (trifluoromethanesulfonates), nonaflates (nonafluorobutanesulfonates), and tresylates (2,2,2,-trifluoroethanesulfonates) have been developed. Triflates react approximately 30,000 times faster than tosylates (10) and tresylates approximately 100 times faster (11). Although the use of these groups can increase the rate of substitution on carbon they do not increase the substrate solubility in water which is the solvent of choice for ionic nucleophiles.

Although these procedures provide an array of methods for the derivatization of alcohols, an alternative which avoids their drawbacks is desirable. In a search for an alternative method the reactions of a new class of compounds, ammonioalkanesulfonate esters, were studied for their applicability. The first examples of this class of compounds were reported by Blumbergs et al.(12) and Sukenik and Bergman (13). Blumbergs et al.prepared methyl and ethyl trimethylammonioalkanesulfonates (n = 2 and 3, see Scheme 3.2) by refluxing betaines in dimethyl or diethyl sulfate in good yields (80 and 65% respectively). The authors showed that these compounds were excellent water soluble alkylating agents. However, it is evident that the synthetic approach of Blumbergs et al.is not suitable for the general application discussed here. Sukenik and Bergman have described the preparation

Scheme 3.2

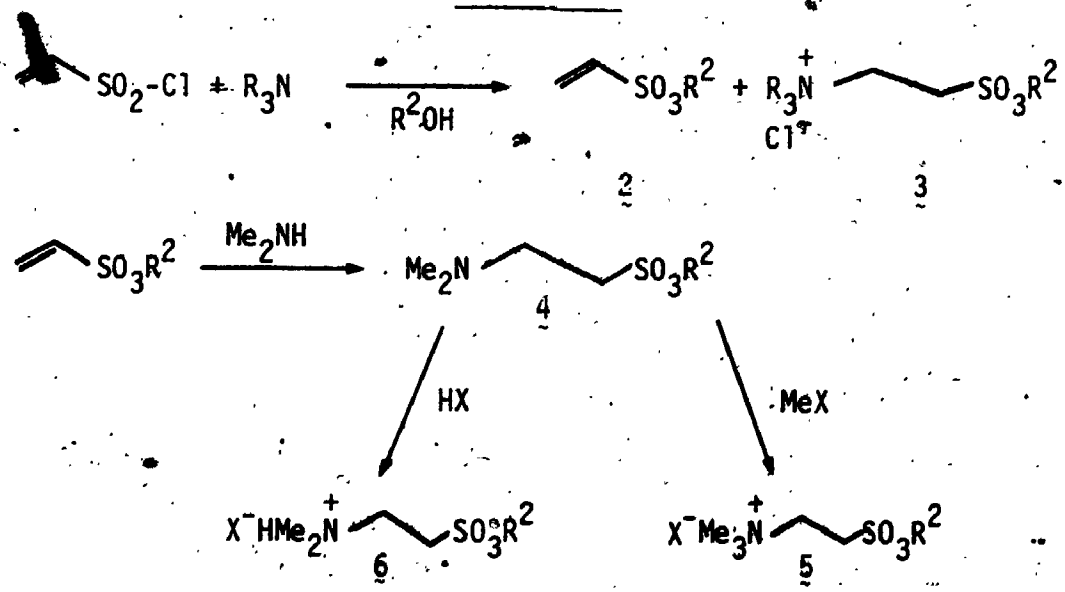


n = 2,3 .

and nucleofugal properties of trimethylammoniobenzenesulfonates (amsylates). These compounds are water soluble and are rapidly hydrolyzed in aqueous solution.

The first reported synthesis of trialkylammonioethanesulfonates applicable to a wide variety of alcohols appeared in 1976 (14). King and Loosmore found that the esters were reactive towards nucleophiles in aqueous solutions. The synthetic route to these esters is summarized in Scheme 3.3. It was found that shaking with aqueous sodium carbonate readily converted 3 to 2 enabling yields of 80 to 100% to be obtained for primary and secondary ethenesulfonate esters, 2. Conversion of 2 to 5 or 6 was essentially quantitative. The first step

Scheme 3.3



X = FSO_3, $MeOSO_3$, CF_3SO_3, I, Br, Cl, p CH_3-$C_6H_4SO_3$, BF_4

of this synthetic sequence is also possible with 2-chloroethanesulfonyl chloride as the starting material (15). The sulfonyl chloride is more convenient as it is commercially available or readily prepared from inexpensive starting materials. Although the synthesis consists of three steps it is typically carried out in one to three hours.

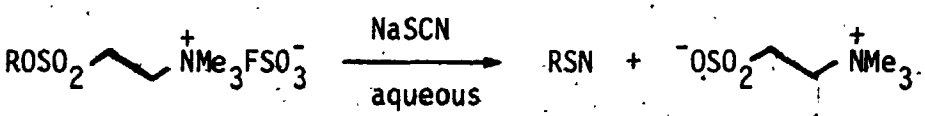
Compounds 5 and 6 will be referred to as alkyl [2]betylates and alkyl [2]norbetylates, respectively. If the presence of a specific counterion is to be indicated, the name of the counterion will simply be appended to the name of the alkyl [2]betylate or alkyl [2]norbetylate. For example the presence of chloride as the counterion for structure 5 would result in using the term alkyl [2]betylate chloride to name the compound. This nomenclature will also be abbreviated to [2]betylate or just betylate when sufficient for the context of the discussion. For betylates with other than two carbons between the ammonio and sulfonyl functions the number in square brackets will define the number of methylenes between these two functionalities.

Alkyl [2]betylates are white crystalline solids, stable at room temperature under anhydrous conditions. Butyl, neopentyl, 1-methylheptyl and 3-phenyl-1-propyl [2]betylates were found to be soluble in water while hexadecyl and docosyl [2]betylates formed a thick emulsion when shaken in water (16). Secondary alkyl [2]betylates were not very stable in water being rapidly hydrolyzed to the alcohol.

It was found that [2]betylates were capable of a wide variety of preparative nucleophilic substitution reactions under a variety of conditions. These will be briefly described at this point. A more detailed description of [2]betylate chemistry, as well as betylate chemistry in general, can be found elsewhere (15-18).

The range of alkyl groups studied with [2]betylates includes butyl as a typical small primary group, hexadecyl and docosyl as large lipophilic groups, neopentyl as a hindered group and 1-methylheptyl as a typical secondary group. The [2]betylates prepared from these alkyl groups produced substitution products with a wide array of anionic and neutral nucleophiles. Primary alkyl [2]betylates underwent clean reaction with azide, bromide, thiocyanate, sulfite, N,N-dimethylthiocarbamate and thiosulfate in water to give the nucleophilic substitution product in greater than 80% yields. The reaction was performed by dissolving or suspending the betylate in water containing a ten fold excess of the reagent. The reaction was essentially complete in 0.5 to 2 h at room temperature and since the leaving group was a betaine (see Scheme 3.4), a simple extraction of the aqueous solvent allowed for convenient workup. This ease of workup and mildness of experimental conditions is one of the strengths of the betylate approach.

Scheme 3.4



Two phase reactions of [2]betylates were also found to be feasible. Under the proper conditions secondary alkyl [2]betylates could also be made to give clean nucleophilic substitution. For primary alkyl [2]betylates the reaction was performed by dissolving the betylate in an appropriate amount of organic solvent and stirring this solution with a ten fold excess of the nucleophile in water at room temperature. The nucleophiles used in this procedure included azide, chloride,

thiourea and N,N-dimethylthiocarbamate. The reaction was generally rapid, in the order of hours and yields were from good to excellent. As before, workup was made convenient and straightforward by the high solubility of the betaine in water. For secondary alkyl [2]betylates the reaction conditions have to be modified to avoid hydrolysis of the betylate to the alcohol. Under two phase reaction conditions with 1.3 molar aqueous sodium thiocyanate approximately 35% 2-octanol was formed. With concentrated aqueous thiocyanate (∿ 8M), alkyl thiocyanate free of alcohol was obtained along with approximately 10% of octenes.

For both of the above modes of reaction, one phase water, and two phase aqueous-organic some nucleophiles did not react cleanly to give good yields of the nucleophilic substitution product. Basic reagents such as acetate, hydrosulfide and ethoxide induced elimination of the elements of trimethylammonium ion to give the alkyl ethenesulfonate (2, see Scheme 3.3). This elimination was also found to occur readily when the pH of the aqueous phase was greater than 6.5 This susceptibility of [2]betylates to basic reagents is a major limitation to their usefulness as substrates in preparative nucleophilic substitutions.

The usefulness of [2]betylates in the conversion of an alcohol to a derivative is due to several factors. These are the low solubility of the betaine leaving group in organic solvents, the large number of different counterions possible with the betylate, and the ability of the betylate cation to act as a phase transfer reagent. A few examples of the application of these factors will be given in the following paragraphs.

In the conversion of a [2]betylate or [2]norbetylate to a sulfonyl chloride the first step was to reflux the betylate with thiourea in 1,2-dimethyoxyethane. During this reaction the betaine leaving group precipitated from solution making it easy to follow the reaction and simplifying the workup since the betaine could be removed by filtration.

The identity of the counterion can be controlled (19) in two ways:

1. the appropriate choice of alkylation (or protonation) reagent in the conversion of an aminoethanesulfonate 4 to the betylate (or norbetylate). For example methylation with trimethyloxonium fluoroborate yields an alkyl [2]betylate fluoroborate. Other counterions introduced by this route include iodide, methylsulfate, fluorosulfate, mesylate and ethenesulfonate. Norbetylates prepared by this route include iodide, bromide, chloride, tosylate and other sulfonates.
2. the exchange of one betylate counterion for another. This can be achieved by ion-pair extraction. For example a betylate fluorosulfate in methylene chloride was shaken with an aqueous solution of sodium hexafluoroantimonate. Separation of the organic layer and evaporation of solvent gave the betylate hexafluoroantimonate.

Control of the identity of the counterion by these methods allows a number of substitutions to be conveniently performed. An example is provided by a convenient synthesis of neopentyl iodide. Nucleophilic displacements at neopentyl carbon are usually carried out only with difficulty. However, alkylation of neopentyl 2-dimethylaminoethane-

sulfonate with methyl iodide followed by reflux of the resulting betylate iodide in DMF gave a good yield of neopentyl iodide in 2 hours (16).

The use of ion-pair extraction has been illustrated by the preparation of hexadecyl picrate from hexadecyl [2]betylate fluorosulfate. The betylate fluorosulfate was dissolved in methylene chloride and shaken with a solution of picric acid in water. This gave the betylate picrate which in turn produced the picryl ether upon refluxing in toluene. The picryl hexadecyl ether was obtained in 75% overall yield. It should be noted that the addition of a trace of picric acid during refluxing in toluene was necessary to prevent elimination of the elements of trimethylammoniun ion to generate hexadecyl ethenesulfonate. This complication does not affect the usefulness of this procedure, however.

These two examples involve what has been defined (15) as substrate-reagent ion-pair reactions (SRIP). A SRIP reaction involves a transformation in which the substrate and the reagent constitute a salt and the reaction is induced by heating the preformed salt in an organic solvent as outlined in Scheme 3.5.

Scheme 3.5

$$ROSO_2CH_2CH_2\overset{+}{N}Me_3Nu^- \xrightarrow{\Delta} R\text{-}Nu + {}^-OSO_2CH_2CH_2\overset{+}{N}Me_3$$

7

The SRIP reaction may also occur at lower temperatures without isolation of the betylate as part of the process which has been defined (15) as stoichiometric phase transfer (SPT). Thus SRIP

reactions are a special case of SPT where the betylate has been isolated and then refluxed to form product. SPT will be described in more detail at a later point in this discussion.

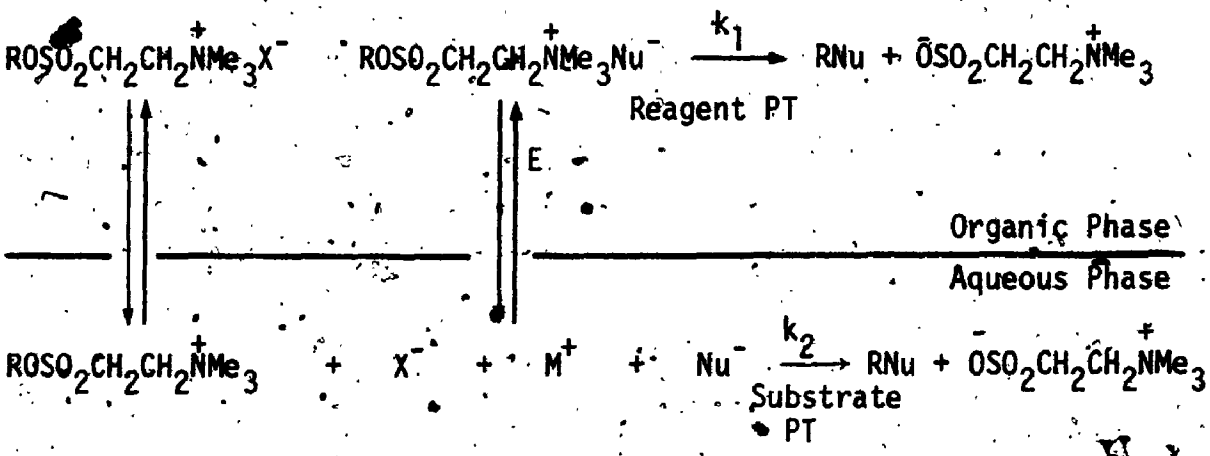
The substrate-reagent ion-pair (SRIP) reaction occurs when the betylate counterion acts as a nucleophile to displace the betaine (7 in Scheme 3.5) and form the product. The advantage of a SRIP procedure is that the reaction can be performed with normally weak nucleophiles such as perchlorate and triflate (15). The reaction is probably made feasible by three factors:

1. poor solvation of the anion in the organic solvents used, the increase in reactivity of poorly solvated anions being well known (20).
2. the insolubility of the betaine.
3. the proximity of the reagent to the substrate due to ion-pairing or higher aggregation.

The substrate phase transfer (SPT) process is outlined in Scheme 3.6. SPT is analogous to catalytic phase transfer. Catalytic phase transfer usually involves the use of a small amount of an ammonium ion to carry a nucleophile from the aqueous phase (as the counterion) of a two phase aqueous-organic solvent system to the organic phase containing the substrate. The anion transported by the ammonium ion is then able to react with the substrate. The leaving group of the substrate is then carried back to the aqueous phase as the new counterion. This process is repeated until the reaction is complete. In stoichiometric phase transfer the phase transfer reagent is the betylate cation, which is consumed during the reaction as it is part of the betaine leaving group. SPT reactions in a system consisting

of two liquid phases can occur in two ways. These are reagent PT and substrate PT (see Scheme 3.6). As outlined in Scheme 3.6 reagent PT is defined as the case in which the nucleophile has been drawn into the organic phase by the ammonio portion of the betylate and product formation occurs there. In substrate PT a betylate molecule has become dissolved in the aqueous phase and undergoes attack by the

Scheme 3.6



$$E = [ROSO_2CH_2CH_2NMe_3Nu^-]/[ROSO_2CH_2CH_2NMe_3][Nu^-]$$

nucleophile to give product.

Despite the high versatility of [2]betylates resulting from their ability to undergo SRIP and SPT reactions with the attendant advantages of these methods, [2]betylates have some inherent disadvantages. These disadvantages, like the advantages, result directly from their structure: These compounds are prone to hydrolysis and to elimination as indicated previously for secondary alkyl [2]betylates.

In order to retain the advantages of the betylate structure in facilitating a wide variety of nucleophilic substitutions and avoid the disadvantages, [3]betylates were prepared and studied during this work.

It was hoped that the inclusion of an extra methylene between the ammonio and sulfonyl function would reduce the rates of hydrolysis and especially elimination without substantially affecting the rate of nucleophilic substitution.

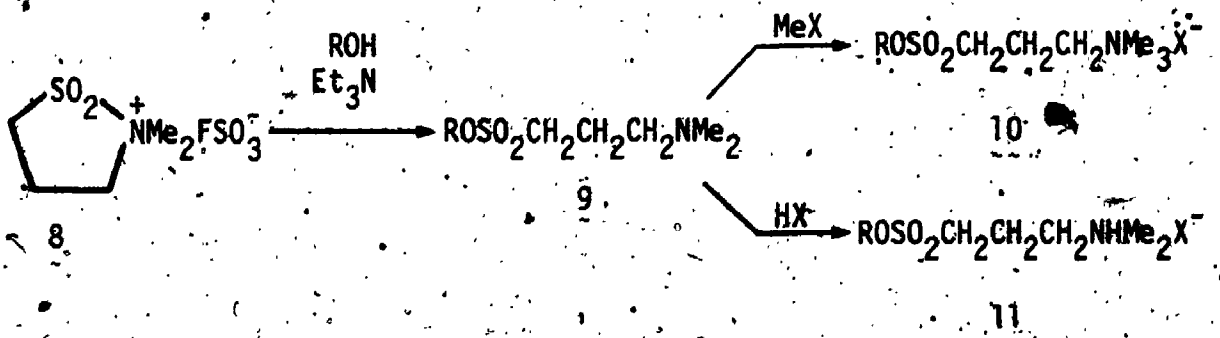
The remainder of this chapter will describe the synthesis and reactions of [3]betylates in the context of their ability to carry out the transformation of an alcohol to a product as outlined in Scheme 3.1.

3.2 Results and Discussion

a) Preparation and Properties of Alkyl [3]Betylates and Norbetylates

The preparation of an alkyl [3]betylate or norbetylate is shown in Scheme 3.7. This two step sequence begins with the reaction of an alcohol with 2,2-dimethylisothiazolidinium fluorosulfate (8). The synthesis of this cyclic sulfonium ion salt and the mechanism of its ring opening with alcohol will be discussed in the next two sections of this chapter.

Scheme 3.7



8 9

The preparation of alkyl N,N-dimethylaminoalkanesulfonates (9) from the cyclic sulfonylammonium salt (8) is straightforward. Alkyl

N,N-dimethylaminoalkanesulfonates (9) will be referred to as alkyl aminoesters or simply as the aminoesters depending on the context of the discussion. The experimental procedure was to add dropwise 1 equivalent of triethylamine to a stirred mixture of 1 equivalent of the cyclic salt and 0.9 eq. of a primary alcohol cooled to less than 4° C with an ice bath. For secondary alcohols 0.5 equivalents of the alcohol were used. The mixture was stirred with cooling for 2-5 h for primary alcohols and 12 h for secondary. Washing of the organic layer with brine followed by drying of the organic layer and evaporation of solvent gave near quantitative (85 - 100%) yields of the desired aminoester. The alkyl aminoesters were used immediately in order to avoid decomposition.

The second step in the preparation of a betylate from the cyclic sulfonylammonium salt (8) is the methylation of the amino function to form a betylate. Methylation was usually performed with methyl fluorosulfate although dimethylsulfate was also efficient. The aminoester was typically dissolved in methylene chloride, the solution cooled to 0° C, and a stoichiometric amount of the methylation agent added. The solution was stirred until product formation appeared complete. Depending on the solubility of the product and the amount of solvent used some precipitation of product was observed. The solvent was removed by evaporation and the product, which often appears as an oil, was triturated with ether until a powder was obtained. The yields obtained for this step ranged from good to quantitative.

The preparation of a norbetylate (11) is analogous to the preparation of a betylate. For example, in the preparation of hexadecyl [3]norbetylate bromide, the aminoester (9) was dissolved in methylene chloride

and anhydrous hydrogen bromide was bubbled through the solution. Evaporation of solvent followed by refluxing in toluene then gave a 69% yield of hexadecyl bromide.

The identity of the counterion of a betylate can be changed by replacement of one betylate counterion with another. For [3]betylates this was originally done to obtain pure samples for combustion analysis because of difficulties encountered in obtaining good analyses for [2]betylate fluorosulfates (19). Betylate fluorosulfates do not recrystallize well and extended storage results in the appearance of a film on the interior of glass containers. This is thought to be a result of decomposition of the fluorosulfate counterion. Anion exchange was used to prepare [3]betylate perchlorates, picrates, acetate fluoride and chloride. Betylate perchlorates and picrates were prepared by adding perchloric or picric acid to an alcohol solution of a betylate fluorosulfate or methylsulfate. Recrystallization of the resulting precipitate gave analytical samples. In contrast to betylate fluorosulfates the betylate perchlorates and picrates obtained were extremely stable to long term storage and easy to purify.

Examples of a betylate acetate, fluoride and chloride were prepared by anion exchange using a resin. For each case Rexyn 201 was loaded with the appropriate anion. For fluoride and acetate this was accomplished by treating the chloride-sulfate form of the resin with aqueous sodium hydroxide until the eluant tested negative for chloride and sulfate. This hydroxide resin was treated with aqueous hydrofluoric acid or acetic acid as needed and washed with water to neutrality. Replacement of the solvent with methanol followed by passing a methanol solution of the betylate through the column resulted in anion

exchange. For chloride, the chloride-sulfate form of the resin was treated with concentrated potassium chloride. The betylate acetate, fluoride and chloride prepared in this manner were not isolated and characterized, their structure was inferred from the high yields of products obtained (91% for the acetate, 67% for the fluoride, and 97% for the chloride) upon removal of the solvent by evaporation and refluxing of the residue in toluene. These two procedures were subsequently applied to [2]betylates (4). It should be noted that the wide variety of counterions which could be introduced to the [2]betylate structure by varying the alkylation agent or by ion-pair extraction can be expected to be available to [3]betylates since both [2] and [3]betylates have the same ammonio function.

A [3]betylate can be obtained from the cyclic sulfonylammonium ion (8) in two steps in near quantitative yields. The synthesis of the cyclic sulfonylammonium ion (8) and its precursor, N-methylpropane-sultam, are described in the next section of this chapter. The sultam, a known compound, was obtainable in 58% yield from commercially available propanesultone by a new three step procedure and converted to the cyclic sulfonylammonium ion (8) in quantitative yield. From this sultam, [3]betylates were obtained in 90% yields resulting in a 52% overall yield of the betylate in six steps from the sultone (12).

The physical and spectral characteristics of [3]betylates and their two immediate precursors are given in Table 3.1.

Table 3.1. Data Summary for [3]Betylates and their Precursors.

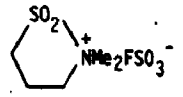
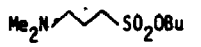
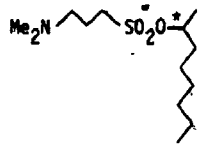
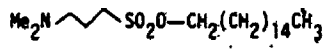
Compound	Physical Characteristics	Spectroscopic Characteristics[a]
	hygroscopic white solid m.p. (seated capillary) 188-189°C	^{1}H nmr (CD_3CN)δ: 2.63 (m,2H), 3.25 (s, 6H), 3.95 (m, 4H)
	liquid	ir ν_{max}: 2955 (m), 2875 (m), 2825 (m), 1460 (m), 1380 (s), 1170 (s), 915 (s) cm^{-1} ^{1}H nmr δ: 1.40 (t, 3H), 2.00 (m, 2H), 2.23 (s, 6H), 2.37 (m, 2H), 3.19 (m, 2H)
	oil	ir ν_{max}: 3061 (w), 3042 (w), 2955 (s), 2878 (m), 2824 (m), 2776 (m), 2729 (w), 1465 (m), 1375 (s), 1168 (s), 940 (s) cm^{-1} ^{1}H nmr δ: 0.96 (t, 3H), 1.44 (m, 2H), 1.71 (m, 2H), 2.03 (m, 2H), 2.12 (s, 6H), 2.33 (m, 2H), 3.19 (m, 2H), 4.23 (t, 2H).
	oil	ir ν_{max}: 2935 (s), 2863 (s), 2824 (s), 2797 (s), 2775 (s), 2728 (w), 1463 (s), 1340 (vs), 1207 (m), 1166 (s), 1120 (m), 1055 (m), 1042 (m), 1031 (m), 955 (vs) cm^{-1} ^{1}H nmr δ: 0.89 (t, 3H), 1.32 (s, 10H), 1.41 (d, 3H), 1.64 (m, 2H), 1.90 to 2.40 (m, 2H), 2.24 (s, 6H), 3.15 (m, 2H), 4.82 (m, 1H)
	low melting solid	ir ν_{max}: 2930 (s), 2859 (s), 2827 (m), 2800 (m), 2779 (m), 2731 (w), 1466 (m), 1358 (s), 1290 (m), 1257 (m), 1209 (m), 1167 (s), 1029 (m), 945 (vs) cm^{-1} ^{1}H nmr δ: 0.88 (t, 3H), 1.27 (s, 26H), 1.73 (m, 2H), 2.01 (m, 2H), 2.22 (s, 6H), 2.39 (t, 2H), 3.16 (m, 2H), 4.18 (t, 2H).

Table 3.1. Continued

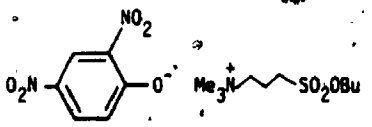
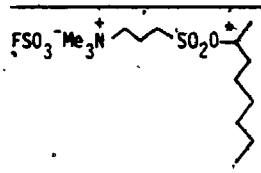
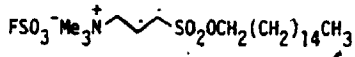
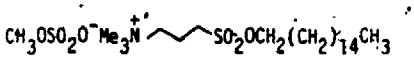
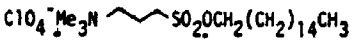
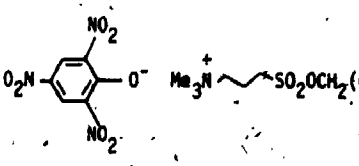
Compound	Physical Characteristics	Spectroscopic Characteristics[a]
$FSO_3^-Me_3\overset{+}{N}\sim\sim SO_2OEt$	solid	ir (KBr disk) ν_{max}: 2970 (w), 1479 (m), 1280 (s), 1165 (s), 1076 (m), 1040 (m), 998 (m), 920 (s), 739 (s) cm^{-1} ^{1}H nmr (CD CN) δ: 1.38 (t, 3H), 2.24 (m, 2H), 3.0 to 3.5 (m, 4H), 3.11 (s, 9H), 4.43 (q, 2H)
$ClO_4^-Me_3\overset{+}{N}\sim\sim SO_2OEt$	white solid mp 95-96.5°C	ir (KBr disk) ν_{max}: 2980 (w), 1478 (m), 1357 (m), 1340 (m), 1304 (m), 1162 (s), 1094 (vs), 995 (m), 912 (s) cm^{-1} ^{1}H nmr (acetone-d_6) δ: 1.49 (t, 3H), 2.46 (m, 2H), 3.39 (s, 9H), 3.43 (m, 2H), 3.74 (m, 2H), 4.38 (q, 2H)
$FSO_3^-Me_3\overset{+}{N}\sim\sim SO_2OBu$	white solid	ir (KBr disk) ν_{max}: 3063 (w), 2962 (m), 2866 (w), 1479 (m), 1282 (vs), 1163 (s), 1074 (m), 932 (s) cm^{-1} ^{1}H nmr (D_2O) δ: 0.93 (t, 3H), 1.40 (m, 2H), 1.77 (m, 2H), 2.36 (m, 2H), 3.17 (s, 9H), 3.49 (m, 4H), 4.39 (t, 2H)
	yellow solid mp 122-123°C	ir (KBr disk) ν_{max}: 2969 (w), 2944 (w), 1639 (s), 1611 (m), 1553 (w), 1639 (s), 1611 (m), 1553 (m), 1506 (m), 1490 (m), 1471 (m), 1435 (m), 1363 (m), 1310 (s), 1290 (m), 1219 (s), 1172 (s), 1160 (m), 950 (m) cm^{-1} ^{1}H nmr (acetone-d_6) δ: 0.93 (t, 3H), 1.43 (m, 2H), 1.72 (m, 2H), 2.51 (m, 2H), 3.48 (s, 9H plus m, 2H), 3.86 (m, 2H), 4.30 (t, 2H), 8.69 (s, 2H).

Table 3.1. Continued

Compound	Physical Characteristics	Spectroscopic Characteristics[2]
	oil	ir ν_{max}: 3064 (w), 2960 (m), 2934 (m), 2862 (w), 1478 (m), 1342 (m), 1289 (s), 1167 (s), 1112 (w), 1069 (s), 910 (s) cm^{-1} ^1H nmr δ: 0.86 (t, 3H), 1.27 (s, 10H), 1.39 (d, 3H), 1.64 (m, 2H), 2.30 (m, 2H), 3.0 - 3.7 (m), 3.20 (s, 9H), 4.80 (m, 1H).
	white solid	ir ν_{max}: 3075 (w), 2972 (s), 2860 (s), 1480 (m), 1363 (m), 1289 (s), 1170 (s), 1072 (s), 951 (m), 925 (m) cm^{-1} ^1H nmr δ: 0.87 (t, 3H), 1.26 (s, 26H), 1.75 (m, 2H), 2.30 (m, 2H), 3.20 (m, 2H), 3.25 (m, 2H), 3.59 (m, 2H), 4.23 (t, 3H).
	white solid	ir ν_{max}: 3050 (w), 2931 (s), 2857 (m), 1477 (m), 1359 (m), 1244 (s), 1167 (m), 1060 (m), 1013 (s), 945 (m); 920 (m), 893 (m) cm^{-1} ^1H nmr δ: 0.88 (t, 3H), 1.26 (s, 26H), 1.75 (m, 2H), 2.31 (m, 2H), 3.27 (s, 9H), 3.38 (m, 2H), 4.27 (t, 2H).
	white solid mp 81-82°C	ir ν_{max}: 3065 (w), 2931 (s), 2858 (m), 1474 (w), 1359 (m), 1168 (m), 1096 (vs), 943 (m), 919 (m), 895 (m) cm^{-1} ^1H nmr δ: 0.88 (t, 3H), 1.27 (s, 26H), 1.76 (m, 2H), 2.33 (m, 2H), 3.21 (s, 9H), 3.31 (m, 2H), 3.59 (m, 2H), 4.27 (t, 2H)
	yellow solid mp 101-102°C	ir (KBr disk) ν_{max}: 2928 (s), 2849 (m), 1628 (s), 1609 (m), 1557 (m), 1479 (m), 1433 (w), 1360 (m), 1330 (s), 1301 (m), 1263 (m), 1071 (w), 943 (m) cm^{-1} ^1H-nmr δ: 0.90 (t, 3H), 1.30 (s, 26H), 1.75 (m, 2H), 2.50 (m, 2H), 3.48 (s, 9H plus m, 2H), 3.86 (m, 2H), 4.90 (t, 2H), 8.70 (s, 2H).

b) Preparation of 2,2-Dimethylisothiazolidinium 1,1-Dioxide Fluorosulfate

Figure 3.1 outlines the preparation of 2,2-dimethylisothiazolidium 1,1-dioxide fluorosulfate (8) from commercially available propanesultone (12) via N-methylpropanesultam (13) whose synthesis has been described by Bliss et al. (21). The first three reactions outlined in Figure 3.1 shows a shortened synthesis of N-methylpropanesultam developed during this study. The yields for these three steps were 94, 93 and 66% respectively resulting in an overall yield of 58% from propanesultone. This compares favorably with the five step procedure of Bliss et al. which gives the N-methylsultam in less than 34% yield in five steps starting from allyl chloride and thioacetic acid.

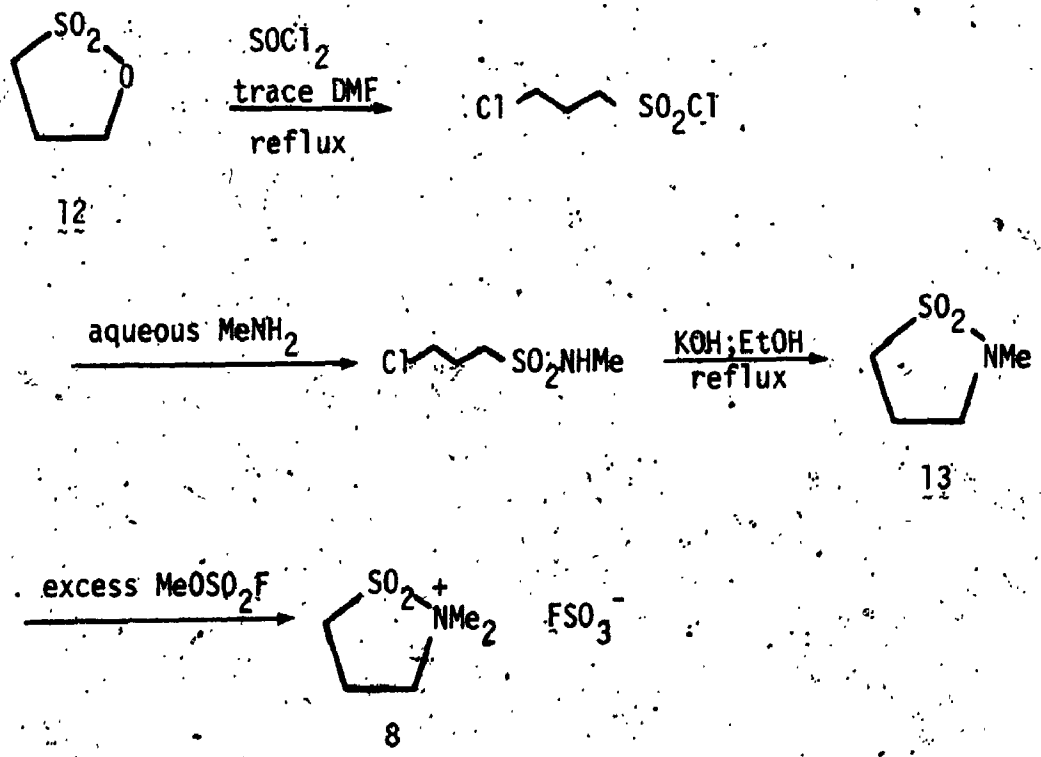


Figure 3.1

Synthesis of 2,2-Dimethylisothiazolidinium 1,1-Dioxide from Propanesultone

The last step in the synthesis of the cyclic sulfonylammonium salt (8) is the methylation of N-methlypropanesultam. This reaction was first performed by Dr. J.R. du Manoir and the product characterized during this work. The methylation of N-methylpropanesultam was accomplished by dissolving the sultam (13) in excess methylfluorosulfate and letting the solution stand until the product precipitated. Since methyl fluorosulfate is acutely toxic this operation was carried out in a well ventilated fume hood. Typically 0.5 to 2 gram of the sultam was dissolved in methyl fluorosulfate and precipitation of the product was noticed almost immediately. After 0.5 h filtration followed by washing with methylene chloride gave a quantitative yield of the cyclic sulfonylammonium salt (8) which was then used immediately for the next step in the betylate synthesis (see Scheme 3.7). Larger scale preparations of the cyclic sulfonylammonium salt (8) were cooled as required during the initial part of the reaction (after solution of sultam had been obtained) to control the reaction which is somewhat exothermic. To prepare the analytical sample or in order to avoid hydrolysis by atmospheric moisture on days of high humidity the salt was prepared in a glove box in a nitrogen atmosphere.

c) Mechanism of Ring Opening of 2,2-Dimethylisothiazolidium 1,1-Dioxide Fluorosulfate (8) with Alcohol and Triethylamine

The ring opening of 2,2-dimethylisothiazolidium fluorosulfate (8) is of mechanistic as well as synthetic interest. This compound is the cyclic analog of the trialkyl (methylsulfonyl) ammonium fluorosulfates used during the work described in chapters 1 and 2. These acyclic

sulfonylammonium salts can react by nucleophilic substitution on the sulfonyl group and by deprotonation to form a zwitterion which then collapses to form sulfene. These two processes are illustrated in Figure 3.2 for the cyclic sulfonylammonium salt (8).

In chapter 2 reaction of diethylmethyl(methylsulfonyl)ammonium fluorosulfate with methanol-d and diethylmethylamine in benzene-acetonitrile was found to occur by both substitution and deprotonation. For the cyclic sulfonylammonium salt (8) several factors can be

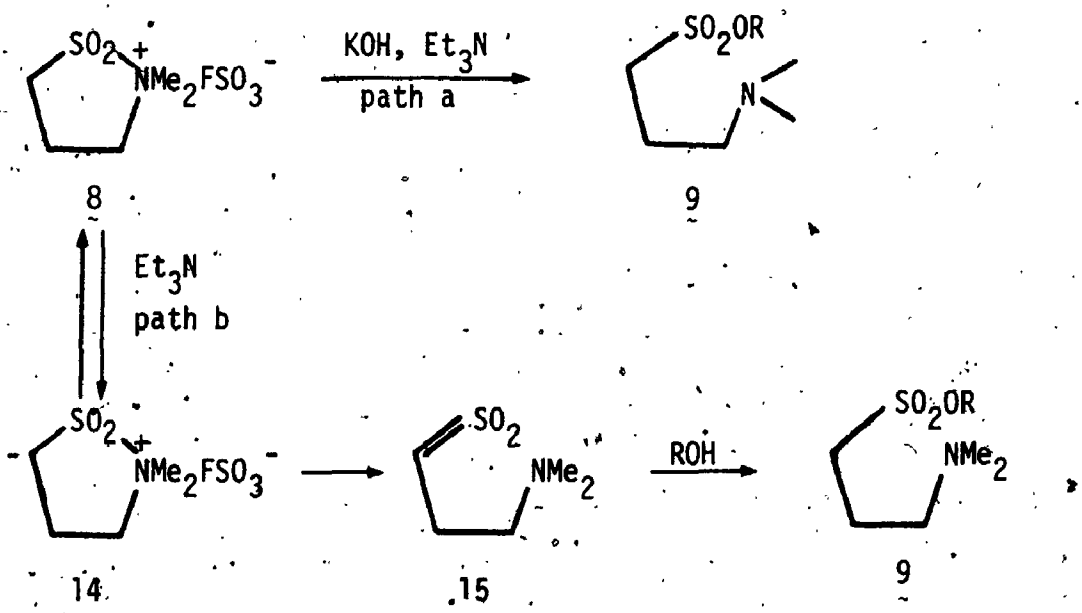


Figure 3.2

Possible Reaction Pathways for the Cyclic Sulfonylammonium salt (8) with Alcohol and Triethylamine

expected to change this pattern on the reaction. These are:

1. For the cyclic compound, nucleophilic substitution can be expected to be much faster than for acyclic sulfonylammonium

salts. This is suggested by results reported in Kaiser's (22) review which state that five-membered ring sulfonates undergo nucleophilic attack six orders of magnitude faster than acyclic sulfonates.

2. The cyclic compound can be estimated to be distinctly less acidic than the acyclic compound. This conclusion is based on the pKa determination by Bordwell et al.(23) in dimethylsulfoxide of dimethylsulfone (28.5) and tetramethylene sulfone (>31).
3. The zwitterion (14), if formed, will be much less likely to form sulfene (15) than an acyclic zwitterion, as this would be what Baldwin (24) has defined as a 5-endo-trig reaction which has been found to be relatively unfavorable, at least for first row elements.

Although extensive studies were not undertaken to investigate the mode of product formation in this reaction some preliminary experiments were done. The reaction of ethanol with the cyclic sulfonylammonium ion (8) in the absence of triethylamine was carried out under the normal experimental conditions used for the synthesis of the aminoester. At the end of 2 h, 56% of starting material was recovered. Workup of solvent did not give aminoester (9). This suggests that the presence of base is necessary for aminoester formation.

To test for deuterium incorporation the normal synthetic procedure (with triethylamine) was carried out with 0.9 eq and 9.0 eq of ethanol-d in two experiments. Although good yields of the ethyl aminoester were obtained neither experiment showed deuterium

incorporation in the nmr of the product. This result was confirmed by two control experiments. In the first the cyclic sulfonylammonium ion (8) was opened with 10 equivalents of ethanol and 1 eq. of triethylamine in the usual manner. Workup gave the ethyl aminoester (9, R = Et). The ethyl aminoester was allowed to stand for 18 h at room temperature to give 73% of the ethyldimethylbetaine whose structure was confirmed by combustion analyses in addition to the usual spectroscopic analysis. In the second control experiment the above procedure was repeated using ethanol-d. Deuterium analysis of the ethyldimethylbetaine by combustion showed 0.00 % excess deuterium in the product. If a sulfene had been formed deuterium incorporation alpha to the sulfonyl group would be expected. If the cyclic sulfonylammonium ion (8) had undergone zwitterion formation (14) hydrogen-deuterium exchange would be expected resulting in deuterium incorporation. These results suggest that the sulfonylammonium ion is opened by nucleophilic attach on sulfur and that this is catalyzed by the base.

d) Synthetic Applications of [3]Betylates

With a variety of betylates in hand it was possible to carry out a number of substitutions with a variety of nucleophiles under several different reaction conditions. The reactions which will be discussed are grouped according to reaction medium and/or synthetic procedure. The groupings are:

(i) one phase aqueous reactions.

(ii) two phase aqueous-organic reactions.

(iij) substrate-reagent ion-pair (SRIP) reactions.

(iv) one phase organic reactions.

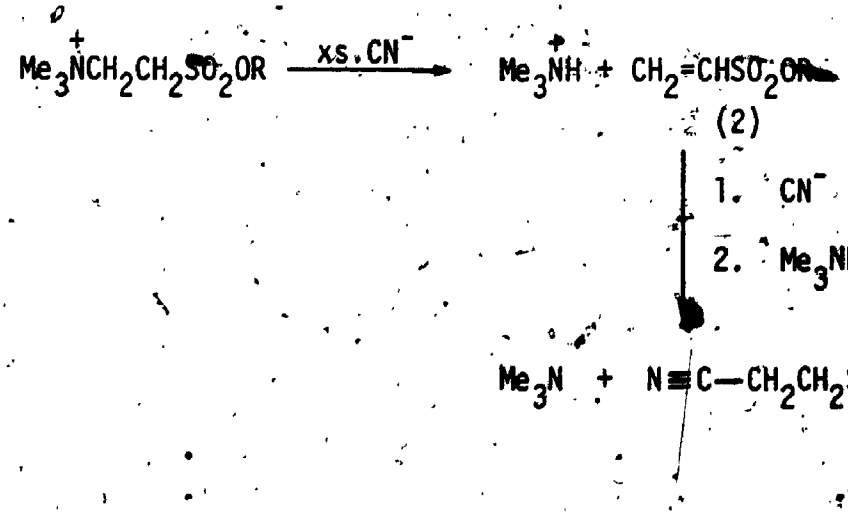
(i) One Phase Aqueous Reactions

The reactions performed in aqueous solvent are summarized in Table 3.2. For these reactions the product of the nucleophilic substitution was not isolated as ethyl thiocyanate is too volatile and the Bunte salt, sodium butyl thiosulfate, is inconvenient to isolate from water. Conversion of the Bunte salt to the sulfonyl chloride by aqueous chlorination resulted in a good yield of product.

(ii) Two Phase Aqueous-Organic Reactions

Tables 3.3 and 3.4 summarize the results obtained for the two phase aqueous-organic reactions of [3]betylates. Inspection of Table 3.3 shows that the choice of organic solvent is not critical for the obtention of good yields. Good to excellent yields were obtained with a variety of nucleophiles including more basic ones such as imidazole, thiophenoxide and cyanide. This is in contrast to [2]betylates which, in the presence of base, revert to ethenesulfonates (2). The ethenesulfonate formed can then undergo conjugate addition to form a Michael adduct as outlined in Scheme 3.8 for cyanide. This process may also be accelerated by the production of trimethylamine

Scheme 3.8



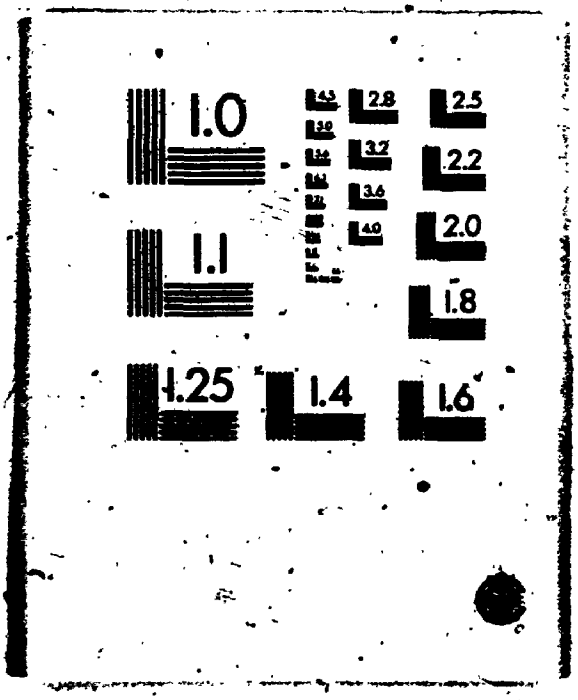

1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.8

Table 3.2 [3]Betylate Reactions in Water

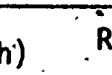
$X^-Me_3\overset{+}{N}(CH_2)_3SO_2OR$

X	R	(mmol)	Reagent(s)	T°C	time h	Product	% Yield
FSO_3	Et	7.75	NaSCN	r.t.	12	EtSCN	66[a]
FSO_3	n-C_4H_9	7.22	$Na_2S_2O_3$	r.t.	12	n-$C_4H_9SO_2Cl$	78[b]
FSO_3	n-C_4H_9	12.9	thiourea	r.t.	12	n-$C_4H_9SO_2Cl$	62[b]

a: Yield estimated by T-60 nmr using methylene chloride as an integration standard. Compound identified by comparison with an authentic sample prepared by the method of Walden (42).

b: Yield of sulfonyl chloride prepared by treating reaction solution with chlorine.

Table 3.3. [3]Betylate Reactions in Two Phase Aqueous-Organic Systems

$X^-Me_3\overset{+}{N}(CH_2)_3SO_2OR$ X	R	(mmol)	Reagent(s)	Medium (T°C, time h)	Product	Yield
FSO_3	butyl	1.1		$CHCl_3$:H_2O (r.t., 17 h)		84
FSO_3	(±)-1-methylheptyl	1.0	NaSPh	$CHCl_3$:H_2O (r.t., 18 h)	RSPh	60
FSO_3	hexadecyl	0.5	NaN_3	CH_2Cl_2:H_2O (r.t., 24 h)	RN_3	100
ClO_4	hexadecyl	0.5	NaI	CH_2Cl_2:H_2O (r.t., 72 h)	RI	90
ClO_4	hexadecyl	0.5	NaSCN	$CHCl_3$:H_2O (r.t., 72 h)	RSCN	93
FSO_3	hexadecyl	0.5	NaSPh	PhH:H_2O (r.t., 18 h)	RSPh	85
FSO_3	hexadecyl	0.5	NaCN	PhH:H_2O (r.t., 72 h)	RCN	95
FSO_3	hexadecyl	0.5	NaBr	PhH:H_2O (r.t., 48 h)	RBr	95

during the formation of the ethenesulfonate. The [3]betylates do not undergo elimination of this type and as will be discussed, give good yields of the substitution product even with such strongly basic species as ethoxide.

The reactions of [3]betylates prepared from R-2-octanol are summarized in Table 3.4. In these reactions approximately 20 to 30 equivalents of the nucleophile were used for each equivalent of betylate. The number of equivalents used for the preparation of the thiocyanate and iodide were estimated to be 32 and 16 respectively. This was based on an 80% conversion of the optically active alcohol to the secondary betylate which is a typical value. For azide 19 equivalents of the nucleophile were used. The solubilities of sodium thiocyanate, azide and iodide are 1.39 g/ml, 0.417 g/ml and 1.84 g/ml respectively (25). The concentrations in g/ml used were 1.16, 0.4 and 1.0 respectively. Comparison of the amounts used with the aqueous solubilities show that the aqueous solutions of the nucleophile were saturated or nearly so. This was done as a result of preliminary experiments with racemic 1-methylheptyl [3]betylate and azide which showed some 2-octanol in the product. The use of more nucleophile was effective in suppressing alcohol formation as it was not detected by either infrared or nmr spectrometry.

The advantage of a [3]betylate over a [2]betylate for the conversions shown in Table 3.4 is illustrated by comparing the reactions of the [2] and [3]betylates derived from R-2-octanol with thiocyanate. With the [2]betylate, octene (16) was detected in addition to the expected thiocyanate. The yield of product after removal of octene and isothiocyanate gave a 50% yield based on alcohol.

Table 3.4. Stereochemistry of Reactions of (R)-1-Methylheptyl [3]Betylate Fluorosulfates.

mmol Betylate[a]	% optical purity[b]	reagent	medium (T°C, time h)	product	% yield[c]	product[d] [α] deg	literature[e] [α] deg	% inversion[l]
(21.0)	94.6	NaSCN	CH_2Cl_2:H_2O (r.t., 15 h)	RSCN	(75)	62.4 83.6	64.7[f] 85.1[g]	102 104
16.5	94.6	NaN_3	CH_2Cl_2:H_2O (r.t., 15 h)	RN_3	85	44.2	45.4[h] 48.1[i]	103 97
(20.0)	94.6	NaI	CH_2Cl_2:H_2O (r.t., 15 h)	RI	(45)	43.7	47.87[f] 48.6[j] 49.7[k]	96 95 94

a: values in parenthesis refer to amount (R)-1-Methylheptyl alcohol used to prepare the betylate. The typical overall yield for conversion of a secondary alcohol to a betylate was 80%.

b: estimated using $[\alpha]_D^{20}$ 9.93 for optically pure 2-octanol (26).

c: yield in parenthesis based on alcohol, (see footnote a).

d: [α] given are $[\alpha]_D$ values determined on neat samples at 21-22°C RSCN, 0.919 (27); RN_3, 0.8555 (28); RI, 1.3219 (26).

e: value taken from Brauns (26) based on $[\alpha]_D$ 9.93. Other values calculated using highest specific rotation obtained in source cited after correction for the optical purity of the alcohol used by the source and the densities listed above.

f: ref. 26

g: ref. 29, $[\alpha]_{546}$

h: ref. 30

i: ref. 31

j: ref. 32

k: ref. 33

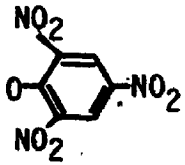
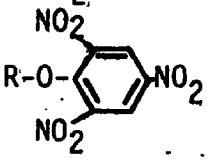
l: % inversion estimated as $[10^4([\ ]\text{ of product})]/[(\%\text{ optical purity of alcohol})(\text{estimated maximum }[\ ]\text{ of product})]$

With the [3]betylate a 75% yield was obtained based on the alcohol. As shown in Table 3.4 all the reactions are highly stereoselective. with inversions in excess of 94%.

(iii) Substrate-Reagent Ion-Pair (SRIP) Reactions

The SRIP reactions performed with [3]betylates are summarized in Table 3.5. These reactions were carried out by refluxing the betylate in an organic solvent followed by evaporation to reduce solvent volume to 2-3 mL. Filtration through silica gel followed by evaporation gave the product in good to excellent yields. The range of nucleophiles used varied from weakly nucleophilic ones such as perchlorate to strong nucleophiles such as bromide. The SRIP reactions generally gave the nucleophilic substitution product resulting from straightforward attack of the anion on the alkyl moiety. The exceptions were the betylate fluorosulfate and methylsulfate. Hexadecyl [3]betylate fluorosulfate gave an 85% yield of dihexadecyl sulfate instead of the expected hexadecyl fluorosulfate. This probably results from hydrolysis of the fluorosulfate anion (34) to sulfate which then attacks the betylate to form hexadecyl sulfate which in turn reacts with another molecule of the betylate to give dihexadecyl sulfate. In agreement with this suggestion Aslam (35) found that hexadecyl [2]betylate bisulfate gave dihexadecyl sulfate on heating. The formation of a mixture of dihexadecyl sulfate and hexadecyl methylsulfate from the reflux of hexadecyl [3]betylate methylsulfate can also be rationalized by preliminary partial hydrolysis of the methylsulfate anion.

Table 3.5. Substrate-Reagent Ion-Pair (SRIP) Reactions of [3]Betylates and [3]Norbetylates

$X^-Me_2R'\overset{+}{N}(CH_2)_3SO_2OR$				Method of			
X	R'	R	mmol	Preparation[a]	Medium (T°C, time h)	Product(s)	Yield[b]
Br	H	hexadecyl	0.61	C	PhMe (110, 2.0)	RBr	70
FSO_3	Me	hexadecyl	0.5	A	PhMe (110, 2.0)	$ROSO_2OR$	85
$MeOSO_2O$	Me	hexadecyl	0.5	A	PhMe (110, 2.0)	$ROSO_2OR$	(70)
						$ROSO_2OMe$	(29)
	Me	hexadecyl	0.65	B(1)	PhMe (110, 3.0)		93
ClO_4	Me	hexadecyl	0.4	B(1)	PhMe (110, 4.0)	$ROClO_3$	32
SCN	Me	hexadecyl	0.4	B(2)	$CHCl_3$ (60, 18)	RSCN	92
Cl	Me	hexadecyl	0.6	B(3)	PhMe (110, 2.0)	RCl	95
CN	Me	hexadecyl	0.6	B(3)	PhMe(110, 2.5)	RCN	(60)
OAc	Me	hexadecyl	4.0	B(3)	PhH (80, 4.0)	ROAc	91
F	Me	hexadecyl	4.0	B(3)	PhMe (110, 72)	RF	67

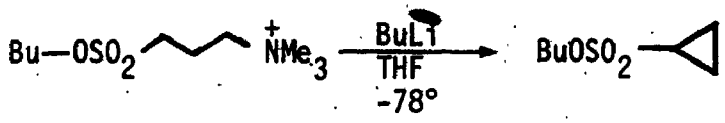
a: Different methods were used to introduce the anion, X^-. (A) Direct introduction during methylation of 9. (B) Ion exchange, either by (1) crystallization (e.g. addition of perchloric acid to an alcoholic solution of the betylate fluorosulfate), (2) ion-pair extraction (e.g. chloroform solution of the betylate fluorosulfate stirred with an aqueous solution of sodium thiocyanate followed by separation of the chloroform layer), (3) Ion exchange in methanolic solution with Rexyn 201. (c) Addition of HX directly to 9.

b: Yields without parentheses refer to isolated yields. Yields within parentheses have been estimated from NMR spectra of the crude products; these materials were not further characterized.

(iv) One Phase Organic Reactions

The last group of reactions attempted are summarized in Table 3.6. The first and last entries are simple nucleophilic substitutions of the reagent on the alkyl moiety. The reactions of the betylates with ethoxide and butyllithium are noteworthy. With hexadecyl [2]betylate fluorosulfate reaction with ethoxide gave hexadecyl 2 ethoxyethane-sulfonate instead of hexadecyl ethyl ether. This result is due to the basicity of ethoxide which causes elimination of the elements of trimethylammonium ion from the [2]betylate to form hexadecyl ethenesulfonate. Michael addition of ethanol to this material gives the observed product. The [3]betylate gave the ether in high yield. Reaction of a [3]betylate with butyllithium, which is of course, a very strong base, does however result in an elimination (see Scheme 3.9) to form a cyclopropanesulfonate ester.

Scheme 3.9

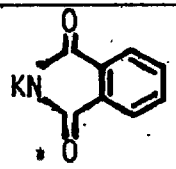
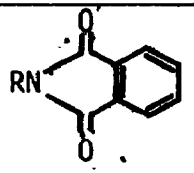


e) Kinetic and Mechanistic Aspects of [3]Betylates

The remainder of this discussion will describe some preliminary kinetic and mechanistic observations made during this study of [3]betylates. As has been shown by the examples given in the previous discussion [3]betylates are quite stable to base induced elimination of trimethylammonium ion. This was best illustrated by the reaction.

Table 3.6. Reactions of [3]Betylates in One Phase Organic Systems.

$X^-Me_3\overset{+}{N}(CH_2)_3SO_2OR$

X	R	(mmol)	Reagent	Medium (T°C, time h)	Product	Yield
FSO_3	Ethyl	3.3		DMF suspension		76
FSO_3	Butyl	1.0	Butyllithium	THF (-78, 2	$ROSO_2$ 	76
ClO_4	Hexadecyl	13.3	NaOEE	EtOH (25, 48)	ROEt	100
FSO_3	Hexadecyl	2.0	$MeNH_2$	DME (25, 24)	RHNMe	60*

a: product isolated and characterized as the base hydrochloride.

of hexadecyl [3]betylate with ethoxide (Table 3.6) which gave only the substitution product. This is in sharp contrast to [2]betylates which are subject to base induced elimination resulting in ethenesulfonate formation. As illustrated in Scheme 3.3 the ethenesulfonate (2) is the precursor to [2]betylates in their synthesis.

The presence of an additional methylene group has an effect on the reactivity of [3]betylates towards substitution in addition to conferring stability towards base in comparison to [2]betylates. The extra methylene damps the effectiveness of the ammonio function to increase the leaving group ability of the sulfonate portion of the betaine. For butyl [2]betylate methylsulfate at 35.0° a k_{obs} of 1.8×10^{-4} s^{-1} (35) has been measured for hydrolysis at pH 4.0 by the pH-stat technique. From the data of Barnard and Robertson (36) a rate constant of 1.13×10^{-5} s^{-1} can be estimated for butyl mesylate. These data indicate that [2]betylates are 16 times more reactive than mesylates.

For the [3]betylate system nmr was used to estimate reaction rates for the hydrolysis of ethyl [3]betylates (both fluorosulfate and perchlorate) and the reaction with thiosulfate. Hydrolysis rates obtained at pH 4 ±.1 in deuterium oxide were approximately 3.6×10^{-5} s^{-1} for the fluorosulfate and 4.2×10^{-5} s^{-1} for the perchlorate. Both of these were run on a T-60 nmr spectrometer at 37°C. Osterman-Golkar et al. (37) obtained a rate constant of 1.7×10^{-5} s^{-1} for the hydrolysis of ethylmesylate in water at 37°C. Since the rate of hydrolysis of mesylates in deuterium oxide has been measured (28) to be approximately 0.93 times as fast as the same rate in water it appears that [3]betylates hydrolyze about 2.5 times

faster than mesylates. Osterman-Golkar et al. also obtained a second order rate constant of 0.55×10^{-3} $M^{-1}s^{-1}$ for the reaction of thiosulfate with ethyl mesylate. Using an XL100 nmr spectrometer a second order rate constant of 1.6×10^{-3} $M^{-1}s^{-1}$ was obtained for the same reaction with ethyl [3]betylate fluorosulfate in deuterium oxide. Assuming that solvent isotope effects are small this indicates that the betylate is only 2.9 times more reactive than the mesylate. Since these rate constants were obtained under less than ideal conditions, these data can only suggest that a [3]betylate is of approximately the same reactivity towards substitution as a mesylate. In comparison with a [2]betylate, a [3]betylate is approximately 5-7 times, or about an order of magnitude, less reactive.

From the kinetic data presented above it can be concluded that the usefulness of a [3]betylate does not arise from any unusually high reactivity imparted by the [3]betaine leaving group but rather from its phase transfer capabilities. This was confirmed by a pair of simple control experiments. A sample of hexadecyl mesylate (0.5 mmol) was dissolved in benzene (5 mL) and a solution of sodium cyanide (5 mmol) in water was added. This two phase mixture was stirred at room temperature for 20 days. After workup 98% of the mesylate was recovered. In contrast to this result the same experiment using a hexadecyl [3]betylate fluorosulfate instead of the mesylate gave 0.020 mmol of the betylate and 0.459 mmol of hexadecyl cyanide after 3 days. Assuming that the betylate and the cyanide were recovered with equal efficiency during the workup these values show that the reaction was 96% complete. The increase in the rate of product formation in the two phase betylate system is therefore a

a result of the ammonio function of the betylate which serves to bring the nucleophile and the substrate together so that reaction can take place. Although a detailed examination of the mechanism of the reaction was not undertaken in this study of [3]betylates the preparation of the hexadecyl thiocyanate by procedure B(2) of Table 3.5 indicates that this reaction proceeds via reagent PT. In this experiment a solution of thiocyanate in water was stirred for 2 h with a solution of the betylate in chloroform. After separation of the two phases the organic layer was refluxed for 18 h. to give a 92% yield of hexadecyl thiocyanate. This result indicates that product formation occurs in the organic phase and that the reaction is therefore a reagent phase transfer process as opposed to a substrate phase transfer.

From the results described to this point it is apparent that [3]betylates can find application to the transformation of an alcohol to a variety of useful products. However, the synthetic scheme employed in this study is somewhat tedious. This has lead to the investigation of:

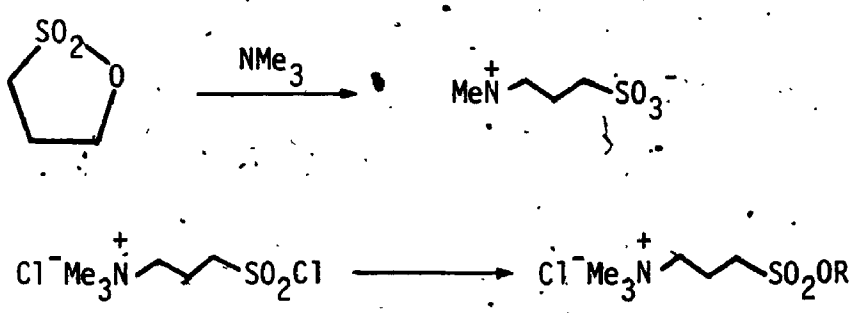
1. a more direct synthesis

and 2. the synthesis of alkyl S-[3]betylates.

The reaction of trimethylamine with propanesultone (see Scheme 3.10) gives the [3]betaine in 92% yield (12). The betaine was then converted to 3-(chlorosulfonyl)-N,N,N-trimethylpropanimium chloride by treatment with thionyl chloride in good yield (70-80%). Reaction of this salt with alcohol using an amine as catalyst should convert the sulfonyl chloride function to a sulfonate ester producing a betylate chloride. Unfortunately this salt is not soluble in non polar aprotic solvents.

As a result this approach was abandoned (39).

Scheme 3.10



The synthesis of alkyl S-[3]betylates has been investigated (40). Two routes were developed (see Figure 3.3) using commercially available propanesultone. The transformations shown in the scheme can be carried out in good yields and the overall yields of S-[3]betylates were better than 85% based on the alcohol. The authors found that S-[3]betylates reactions with nucleophiles occurred in good yields under mild conditions and that in reactions with basic reagents such as ethoxide, thiophenoxide, methylamine and cyanide the S-[3]betylates were similar to N-[3]betylates. Unfortunately S-[3]betylates are prone to dealkylation reactions of the sulfonio group. Examples of dealkylation found by the authors were the formation of 15% methyl picryl ether during the reflux of hexadecyl S-[3]betylate picrate and the deethylation of a neopentyl S-[3]betylate with two ethyl groups (see Scheme 3.12) on the sulfonio sulfur when reacted with thiophenoxide. Also, in the latter reaction some product was obtained which most likely arose from substitution at the carbon of the betaine chain next to the sulfonio group.

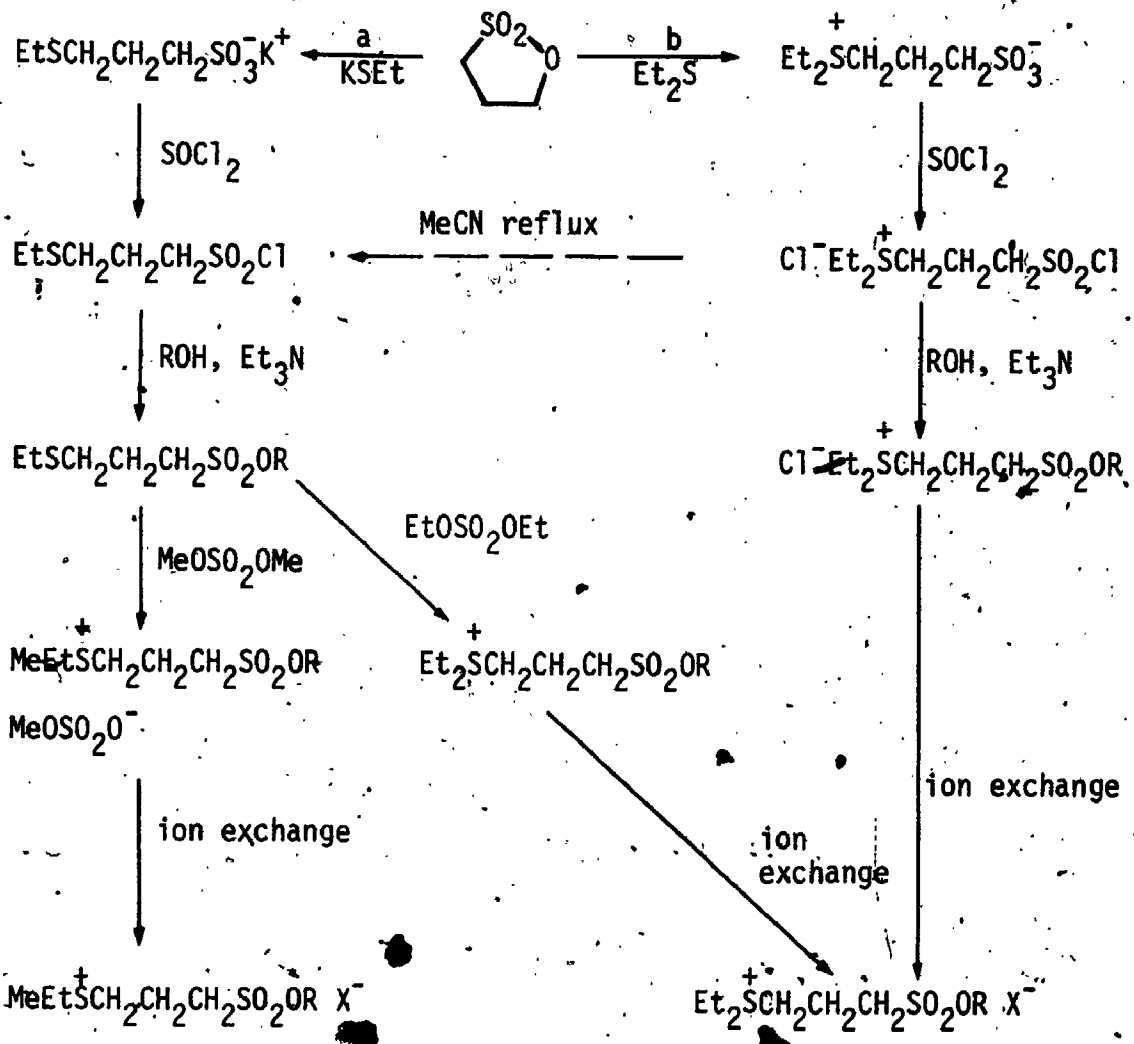


Figure 3.3.

Synthetic Approaches to Alkyl S-[3]Betylates

Scheme 3.12

$$Me_3CCH_2OSO_2CH_2CH_2CH_2\overset{+}{S}Et_2 \xrightarrow{NaSPh}$$

$$PhSEt + Me_3CCH_2OSO_2CH_2CH_2CH_2SEt + Me_3CCH_2OSO_2CH_2CH_2CH_2SPh$$

These results show that dealkylation and/or substitution on the betaine portion of S-[3]betylates are side reactions which limit the usefulness of the S-[3]betylates.

3.3 Conclusions

1. [3]Betylates can be used as intermediates to transform primary and secondary alcohols to a wide variety of products.
2. [3]Betylate reactions are characterized by mild reaction conditions, convenient workup and good yields.
3. [3]Betylates react in homogeneous media at approximately the same rate as mesylates and approximately an order of magnitude more slowly than [2]betylates.
4. [3]Betylates give clean nucleophilic substitutions with strong bases. Elimination could however be effected with butyllithium. This is in contrast to [2]betylates which give elimination with such weakly basic reagents such as acetate and hydrosulfide.
5. The chief drawback to the application of [3]betylates is their synthesis.

3.4 Experimental

Infrared (ir) spectra were recorded on a Perkin-Elmer 621 Grating infrared spectrophotometer unless otherwise noted. The ir spectra were run in CH_2Cl_2 using 0.1 mm NaCl or KBr cells unless otherwise specified and calibrated against the polystyrene peak at 1601.9 cm^{-1}. Nuclear magnetic resonance (nmr) spectra were run in $CDCl_3$ unless otherwise specified using a Varian T-60 or XL-100 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as an internal standard for ^{1}H nmr and ^{13}C nmr and trichlorofluoromethane for ^{19}F nmr. Mass spectra (ms) were determined on a Varian MAT 311A spectrometer. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Rotations were determined with a Rudolph Model 80 polarimeter using sodium or mercury light source.

Benzene, toluene (Fisher) and 1,2-dimethoxyethane (Eastman) were dried by distillation from calcium hydride. Acetonitrile was dried by distillation from phosphorus pentoxide. All these solvents were stored over molecular sieves (Fisher 3Å grade 564, 8-12 mesh) dried for 3 h at 320°C. All other solvents were reagent grade (Fisher) unless otherwise specified. Organic extracts were dried over anhydrous magnesium sulfate (Fisher, certified grade). Solvents were evaporated under reduced pressure using a rotary evaporator connected to a water aspirator. The "short path distillation" apparatus used was essentially a cold finger sublimation apparatus, except that it has two wells in the bottom, one being used as the still pot and the other as the receiver. The cold finger was oriented so that the

liquid dripped directly into the receiving well. The distance between the tip of the cold finger and the lowest portion of the liquid being distilled was 3 cms. This apparatus has been described previously as the cold finger distillation apparatus (41).

Thionyl chloride, 1-butanol, hexadecyl alcohol (sold as cetyl alcohol) were purchased from Fisher Scientific Company Ltd. The resin used for ion exchange experiments, Rexyn 201 (chloride-sulfate form), was also purchased from Fisher Scientific Company. ℓ-2-Octanol and methyl fluorosulfate (sold as Magic Methyl) were purchased from Aldrich Chemical Company. Magic Methyl was distilled under anhydrous conditions before use.

Elemental microanalysis were performed by Microanalysis Laboratories Ltd. formerly of Toronto and Thornhill now located at Markham, Ontario, Canada and Guelph Chemical Laboratories Ltd. of Guelph, Ontario, Canada. Deuterium combustion analysis was performed by Josef Nemeth of Urbana, Illinois, U.S.A.

The Preparation of Alkyl 3-(Dimethylamino)-propanesulfonates (9)

a) Preparation of Ethyl 3-(dimethylamino)propane-1-sulfonate

To a stirred mixture of 2.2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate (5.5 g, 22.08 mmol) and absolute ethanol (760 mg, 16.17 mmol) in methylene chloride (20 mL) at 0° C, triethylamine (2.2 g, 21.78 mmol) was added. The reaction mixture was stirred for 2 h, washed with brine, dried and evaporated to give a liquid

(100%) ir ν_{max}: 2955 (m), 2875 (m), 2825 (m), 1460 (m), 1350 (s), 1170 (s), 915 (s) cm^{-1}; ^1H nmr δ: 1.40 (t, 3H), 2.00 (m, 2H), 2.23 (s, 6H), 2.37 (M, 2H), 3.19 (m, 2H), 4.30 ppm (q, 2H). The product was used without further purification to avoid decomposition.

A duplicate experiment without triethylamine gave a 56% recovery of starting material after 2 h. No product was obtained from the reaction.

b) Preparation of Butyl 3-(dimethylamino)propane-1-sulfonate

To a stirred mixture of 2,2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate (2.77 g, 11.1 mmol) and 1-butanol (.630 g, 8.5 mmol) in methylene chloride (30 mL) at 0° C, triethylamine (1.13 g, 11.2 mmol) was added. The reaction mixture was stirred for 4 h, washed with brine, dried and evaporated to give an oil)1.72 g, 91%); ir ν_{max}: 3061 (w), 3042 (w), 2955 (s), 2878 (m), 2824 (m), 2776 (m), 2729 (w), 1465 (m), 1357 (s), 1168 (s), 940 (s) cm^{-1}; ^1H nmr δ: 0.96 (t, 3H), 1.44 (m, 2H), 1.71 (m, 2H), 2.03 (m, 2H), 2.12 (s, 6H), 2.33 (m, 2H), 3.19 (m, 2H), 4.23 (t, 2H). This material was used without further purification.

c) Preparation of R-(-)-1-Methylheptyl and Racemic 1-Methylheptyl 3-(Dimethylamino)propanesulfonates

To a stirred mixture of 2,2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate (10.1 g, 40.6 mmol) and commercial ℓ-2-octyl alcohol (94.6% optically pure, 2.6 g, 20.3 mmol) at 0° C, trimethylamine

(4 g, approx. 1 eq.) was added. The mixture was stirred overnight in a cold room (approx. 4° C). The solution obtained was washed in aqueous sodium carbonate, water, dried and evaporated to give the produce as an oil (5.02 g, 89%) ir ν_{max}: 2935 (s), 2863 (s), 2824 (s), 2797 (s), 2775 (s), 2728 (w), 1463 (s), 1340 (vs), 1207 (m), 1166 (s), 1120 (m), 1055 (m), 1042 (m), 1031 (m), 955 (vs) cm^{-1}; ^1H nmr δ: 0.89 (t, 3H), 1.32 (s, 10H), 1.41 (d, 3H), 1.64 (m, 2H), 1.90 to 2.40 (m, 2H), 2.24 (s, 6H), 3.15 (m, 2H), 4.82 (m, 1H). The same procedure was used for the racemic alcohol.

d) Preparation of Hexadecyl 3-(dimethylamino)propane sulfonate

To a stirred mixture of 2,2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate (687 mg, 2.76 mmol) and hexadecyl alcohol (605 mg, 2.50 mmol) in methylene chloride (20 mL) at 0° C, triethylamine (288 mg, 2.85 mmol) was added. The mixture was stirred for 4 h, washed with water, dried and the solvent removed by evaporation to give the product as a low melting white solid (848 mg, 87%); ir ν_{max}: 2930 (s), 2859 (s), 2800 (m), 2827 (m), 2779 (m), 2731 (w), 1466 (m), 1358 (s), 1290 (m), 1257 (m), 1209 (m), 1167 (s), 1029 (m), 945 (vs) cm^{-1}; ^1H nmr δ: (t, 3H), 1.27 (s, 26H), 1.73 (m, 2H), 2.01 (m, 2H), 2.22 (s, 6H), 2.39 (t, 2H), 3.16 (m, 2H), 4.18 (t, 2H). This material was used without further purification.

The Preparations of the 3-(Alkoxysulfonyl)-N,N,N-trimethyl-propanaminium salts (Alkyl [3]Betylates)

a) Preparation of 3-(Ethoxysulfonyl)-N,N,N,-trimethylpropanaminium fluorosulfate (Ethyl [3]Betylate Fluorosulfate)

To a stirred solution of ethyl 3-(dimethylamino)propanesulfonate (3.12 g, 16.00 mmol) in methylene chloride (20 mL) at 0° C, methyl fluorosulfate (1.30 mL 1 eq.) was added and the solution allowed to stir for 1 h. After evaporation of solvent and titration of the oil with ether a white solid was obtained by filtration (3.8 g, 78%); ir (KBr disk) ν_{max}: 2970 (w), 1479 (m), 1280 (s), 1165 (s), 1076 (m), 1040 (m), 998 (m), 920 (s), 739 (s) cm^{-1}; ^1H nmr (CD_3CN) δ: 1.38 (t, 3H), 2.24 (m, 2H), 3.0 to 3.5 (m, 4H), 3.11 (s, 9H), 4.43 (q, 2H).

b) Preparation of 3-(Ethoxysulfonyl)-N,N,N,-trimethylpropanaminium perchlorate (Ethyl [3]Betylate Perchlorate)

To ethyl [3]betylate fluorosulfate (6.3 g, 20.4 mmol) dissolved in warm absolute ethanol excess aqueous perchloric acid (70%) was added. On cooling to room temperature a precipitate (5.7 g, 90%) was obtained. The precipitate was recrystallized from absolute ethanol to give needles, mp 95-96.5° C, lit. mp 95.5-96.5° C (12); ir (KBR disk) ν_{max}: 2980 (w), 1478 (m), 1357 (m), 1340 (m), 1304 (m), 1162 (s), 1094 (vs), 995 (m), 912 (s) cm^{-1}; ^1H (acetone - d_6) δ: 1.49 (t, 3H), 2.46 (m, 2H), 3.39 (s, 9H), 3.43 (m, 2H), 3.74 (m, 2H), 4.38 (q, 2H). Anal. calcd. for $C_8H_{20}NClO_7S$: C 31.02, H 6.51, N 4.52, Cl 11.45, S 10.35; found C 31.06, H 6.78, N 4.38, Cl 11.57, S 10.24.

c) Preparation of 3-(Butoxysulfonyl)-N,N,N-trimethylpropanaminium Fluorosulfate (Butyl [3]Betylate Fluorosulfate)

To a stirred solution of butyl 3-(dimethylamino)propanesulfonate (1.72 g, 6.89 mmol) in methylene chloride (10 mL) at 0° C methyl fluorosulfate (0.56 mL, 1 eq.) was added. Precipitation of product was observed almost immediately and the reaction mixture was allowed to stir for 1 h. Evaporation of solvent and trituration with ether gave a white solid after filtration (2.31 g, 99%); ir (KBr disk) ν_{max}: 3063 (w), 2962 (m), 2866 (w), 1479 (m), 1282 (vs), 1163 (s), 1074 (m), 932 (s) cm^{-1}; ^1H nmr (D_2O) δ: 0.93 (t, 3H), 1.40 (m, 2H), 1.77 (m, 2H), 2.36 (m, 2H), 3.17 (s, 9H), 3.49 (m, 4H), 4.39 (t, 2H).

d) Preparation of 3-(Butoxysulfonyl)-N,N,N-trimethylpropanaminium Picrate (Butyl [3]Betylate Picrate)

Butyl [3]betylate fluorosulfate (1.5 g, 4.45 mmol) was dissolved in warm ethanol (15 mL) and picric acid (1.3 g, 1.3 eq.) was added. On cooling to room temperature yellow crystals were obtained. Repeated recrystallization from warm ethanol gave an analytical sample (m.p. 122-123° C); ir (KBr disk) ν_{max}: 2969 (w), 2944 (w), 1639 (s), 1611 (m), 1553 (m), 1506 (m), 1490 (m), 1471 (m), 1435 (m), 1363 (s), 1310 (s), 1290 (m), 1219 (s), 1172 (s), 1160 (m), 950 (m) cm^{-1}; ^1H nmr (acetone - d_6) δ: 0.93 (t, 3H), 1.43 (m, 2H), 1.72 (m, 2H), 2.51 (m, 2H), 3.48 (s, 9H plus m, 2H), 3.86 (m, 2H), 4.30 (t, 2H), 8.69 (s, 2H). Anal. calcd. for $C_{16}H_{26}N_4O_{10}S$: C 41.20, H 5.62, N 12.01, S 6.87; found C 40.98, H 5.77, N 12.21, S 6.69.

e) Preparation of (R)-N,N,N,-Trimethyl-3-[(1-methylheptyl)oxy] sulfonyl]propanaminium Fluorosulfate and Racemic 3-(1-methyl-heptyloxysulfonyl)- N,N,N-trimethylpropanaminium Fluorosulfate ((R)-1-Methylheptyl [3]Betylate Fluorosulfate and 1-Methylheptyl [3] Betylate Fluorosulfate)

To a stirred solution of R-(-)-1-methylheptyl 3-(dimethylamino)-propanesulfonate (5.02 g, 18.0 mmol) in methylene chloride at 0° C (30 mL), methyl fluorosulfate (1.45 mL, 1 eq.) was added. The solution was stirred for 1 h and evaporated to give an oil (6.33 g, 89%); ir ν_{max}: 3064 (w), 2960 (m), 2934 (m), 2862 (w), 1478 (m), 1342 (m), 1289 (s), 1167 (s), 1112 (w), 1069 (s), 910 (s) cm^{-1}; ^1H nmr δ: 0.86 (t, 3H), 1.27 (s, 10H), 1.39 (d, 3H), 1.64 (m, 2H), 2.30 (m, 2H), 3.0 - 3.7 (m), 3.20 (s, 9H), 4.80 (m, 1H). The racemic material was prepared in the same manner and both were used without further purification.

f) Preparation of 3-(Hexadecyloxysulfonyl)-N,N,N-trimethyl-propanaminium fluorosulfate (Hexadecyl [3]Betylate Fluorosulfate)

To a stirred solution of hexadecyl 3-(dimethylamino)propanesulfonate (3.81 g, 9.75 mmol) in methylene chloride (40 mL) at 0° C, methyl fluorosulfate (0.80 ml, 9.9 mmol) was added. After 1 h the solvent was removed by evaporation to give a white mass which was triturated with ether. Filtration gave a white solid (4.5 g, 91%); ir ν_{max}: 3075 (w), 2972 (s), 2860 (s), 1480 (m), 1363 (m), 1289 (s), 1170 (s), 1072 (s), 951 (m), 925 (m) cm^{-1}; ^1H nmr δ: 0.87 (t, 3H), 1.26 (s, methylene absorptions), 1.75 (m, 2H), 2.30 (m, 2H), 3.20 (s, 9H),

3.25 (m, 2H), 3.59 (m, 2H), 4.23 (t, 2H). This material was used without further purification.

g) Preparation of 3-(Hexadecyloxysulfonyl)-N,N,N-trimethyl-propanaminium Methylsulfate (Hexadecyl [3]Betylate Methylsulfate)

To a solution of hexadecyl 3-(dimethylamino)propanesulfonate (5.4 g, 13.8 mmol) in methylene chloride (30 mL) at 0° C, dimethylsulfate (1.75, 1 eq,) was added. The solution was stirred for 2 h and the solvent removed by evaporation to give an oil. The oil was triturated with ether-petroleum ether (bp 30-60°) to give a white solid (5.25 g, 74%); ir ν_{max}: 3050 (w), 2931 (s), 2857 (m), 1477 (m), 1359 (m), 1244 (s), 1167 (m), 1060 (m), 1013 (s), 945 (m), 920 (m), 893 (m) cm^{-1}; ^1H nmr δ: 0.88 (t, 3H), 1.26 (s, methylene absorptions), 1.75 (m, 2H), 2.31 (m, 2H), 3.27 (s, 9H), 3.38 (m, 2H), 4.27 (t, 2H). This material was used without further purification.

h) Preparation of 3-(Hexadecyloxysulfonyl)-N,N,N,-trimethyl-propanaminium Perchlorate (Hexadecyl [3]Betylate Perchlorate)

To hexadecyl [3]betylate methylsulfate (1.30 g, 2.51 mmol) dissolved in warm methanol, 70% perchloric acid was added until precipitation appeared complete. Filtration gave hexadecyl [3]betylate perchlorate (1.25 g, 98%). Repeated recrystallization from absolute ethanol gave an analytical sample, mp 81-82° C; ir ν_{max}: 3065 (w), 2931 (s), 2858 (m), 1474 (w), 1359 (m), 1168 (m), 1096 (vs), 943 (m), 919 (m), 895 (m) cm^{-1}; ^1H nmr δ: 0.88 (t, 3H), 1.27 (s, 26H), 1.76 (m, 2H), 2.33 (m, 2H), 3.21 (s, 9H), 3.31 (m, 2H), 3.59 (m, 2H),

4.27 (t, 2H). Anal. calcd. for $C_{22}H_{48}NClO_7S$: C 52.21, H 9.56, N 2.77, Cl 7.00, S 6.33; found C 51.96, H 9.54, N 3.03, Cl 7.55, S 6.90.

i) Preparation of 3-(Hexadecylcoxysulfonyl)-N,N,N-trimethyl-propanaminium picrate (Hexadecyl [3]Betylate Picrate)

Hexadecyl [3]betylate fluorosulfate (2.0 g, 3.96 mmol) was dissolved in warm ethanol (20 mL) and picric acid (1.3 g, 1.4 eq.) was added. A yellow precipitate (2.35 g, 95%) was obtained on cooling to room temperature. Repeated recrystallization from ethanol gave an analytical sample, mp 101-102° C; ir (KBr disk) ν_{max}: 2928 (s), 2849 (m), 1628 (s), 1609 (m), 1557 (m), 1479 (m), 1433 (w), 1360 (m), 1330 (s), 1301 (m), 1263 (m), 1071 (w), 943 (m) cm^{-1}; ^1H nmr δ: 0.90 (t, 3H), 1.30 (s, 26H), 1.75 (m, 2H), 2.50 (m, 2H), 3.48 (s, 9H plus m, 2H), 3.86 (m, 2H), 4.90 (t, 2H), 8.70 (s, 2H). Anal. calcd. for $C_{28}H_{50}N_4O_{10}S$: C 52.98, H 7.94, N 8.83, S 5.05; found C 52.86, H 7.91, N 8.71, S 4.89.

The Synthesis of 2,2-Dimethylisothiazolidinium 1,1-Dioxide Fluorosulfate (8)

a) Preparation of 3-Chloropropane-1-sulfonyl Chloride

A mixture of 1,3-propanesultone (200 g, 1.64 mol) and thionyl chloride (400 g, 3.36 mol) with dimethylformamide (approx. 1 mL) was refluxed overnight. The excess thionyl chloride was removed by distillation and the product obtained as a pale yellow liquid by distillation at reduced pressure, $bp_{0.55}$ 102-104°C (272 g, 94%); ir ν_{max}: 3065 (w), 3000 (w), 2972 (w), 2925 (w), 2876 (w), 1443 (m), 1369 (s), 1356 (m), 1311 (w), 1192 (m), 1170 (s), 1026 (w), 963 (w), 860 (w) cm^{-1}; ^1H nmr δ: 2.49 (m, 2H), 3.84 (m, 4H). The spectra were identical to those of an authentic sample prepared by the method of Bliss et al (21) except that the nmr spectrum of the latter showed a small doublet at 1.73 ppm presumably due to impurity.

b) Preparation of N-Methyl-3-Chloropropane-1-sulfonamide

To a solution of 3-chloropropanesulfonyl chloride (50 g, .28 mol) in ether (50 mL) at 0°C, an aqueous solution of methylamine (40%, 60 mL) was added dropwise. The organic phase was dried and the solvent removed to give an oil (4.5 g, 93%); ir ν_{max}: 3393 (m), 3310 (broad, w), 3061 (w), 2969 (w), 2939 (w), 1444 (w), 1397 (m), 1328 (s), 1260 (w), 1152 (s), 1129 (m), 1074 (m), 874 (m), 838 (m) cm^{-1}; ^1H nmr δ: 2.18 (m, 2H), 2.79 (s, 3H), 3.13 (m, 2H), 3.73 (t, 2H), 4.76 (broad, 1H).

c) Preparation of N-Methylpropanesultam

N-Methyl 3-chloropropanesulfonamide (45 g, 0.26 mol) was dissolved in absolute ethanol (150 mL) freshly distilled from potassium hydroxide and added dropwise to a refluxing solution of potassium hydroxide (15 g, .27 mol) in absolute ethanol (150 mL, distilled from KOH) over 1.5 h. The reaction mixture was refluxed for a further 15 min. and kept basic by addition of a small amount of potassium hydroxide. The reaction mixture was cooled, acidified with concentrated hydrochloric acid, dried and the solvent removed by evaporation to give a gold colored liquid which was recrystallized from ether-petroleum ether (bp 30-60°) with charcoal to give white crystals (23.3 g, 66%); m.p. 46-49°, lit. 45-47° (17); ir ν_{max}: 3058 (w), 2967 (w), 2945 (w), 2883 (w), 2866 (w), 1308 (s), 1257 (m), 1239 (w), 1187 (m), 1143 (s), 1128 (s), 1047 (w), 1015 (w), 994 (m) cm^{-1}; ^1H nmr 2.34 (m, 2H), 2.68 (s, 3H), 3.19 (t, 2H), 3.24 ppm (t, 2H). The spectra were identical to those of an authentic sample prepared by the method of Bliss et al.(21) and a mixed melting point showed no depression.

d) Preparation of 2,2-Dimethylisothiazolidinium 1,1-Dioxide Fluorosulfate

In a well ventilated fume hood, N-methylpropanesultam (0.97 g, 7.2 mmol) was dissolved in excess methyl fluorosulfate. Precipitation was observed almost immediately. After 0.5 h the product was collected by vacuum filtration and washed with methylene chloride to give white crystals (1.8 g, 98%). This material was used without further

purification for the preparation of alkyl-3-(dimethylamino)propane-sulfonates. On days of high humidity the preparation was carried out in a glove box. Larger scale reactions (3-5 g) were cooled initially with an ice-water bath. The analytical sample was prepared in a glove box by recrystallization from dry acetonitrile-methylene chloride, which gave crystals mp 188-189° C (sealed capillary); ^{1}H nmr (CD_3CN) δ: 3.95 (m, 4H), 3.25 (s, 6H), 2.63 (m, 2H). Anal. calcd. for $C_5H_{12}FNO_5S_2$: C 24.09, H 4.85, N 5.62, S 25.72; found C 23.86, H 4.91, N 5.49, S 25.56.

Ring Opening Reactions of 2,2-Dimethylisothiazolidium Fluorosulfate with Ethanol-d and Triethylamine

The reaction of 2,2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate was carried out in the usual manner used to prepare alkyl 3-(dimethylamino)propane-1-sulfonates except that 0.9 eq. of ethanol-d was used. The product obtained did not show any sign of deuterium incorporation as measured by T-60 nmr. Another experiment using 9.0 eq of ethanol-d also did not give any sign of deuterium incorporation in the T-60 nmr.

As a control, the experiment was repeated using 10 eq. of ethanol-d. The product obtained was allowed to stand overnight at room temperature to give N,N,N-dimethylethylpropane sulfobetaine (73%): ^{1}H nmr (D_2O-DSS) 1.35 (m, 3H), 2.22 (m, 2H), 2.99 (t, 2H), 3.08 (s, 6H), 3.92 (m, 4H). Deuterium combustion analysis showed no deuterium incorporation and the sample was identical to an authentic sample prepared by the same method.

Reactions of 3-(Alkoxysulfonyl)-N,N,N-trimethylpropanaminium salts (Alkyl [3]Betylates) in Water

a) Preparation of Ethyl Thiocyanate

Ethyl [3]betylate fluorosulfate (2.40 g, 7.75 mmol) was dissolved in a concentrated aqueous solution of sodium thiocyanate (40 mL) and allowed to stand overnight. The solution was extracted with carbon tetrachloride and the yield (66%) estimated by nmr (T-60) of the organic phase using methylene chloride as an integration standard; ir ν_{max}: 2992 (m), 2978 (m), 2876 (w), 2845 (w), 2160 (vs), 1448 (s), 1372 (m), 1272 (s), 1061 (w), 968 (m) cm^{-1}; ^1H nmr (CCl_4, acetone-d_6 as internal standard) δ: 1.53 (t, 3H), 3.05 (q, 2H). The spectra were identical to those of an authentic sample prepared by the method of Walden (42).

b) Preparation of 1-Butanesulfonyl Chloride Using Sodium Thiosulfate

Butyl [3]betylate fluorosulfate (2.44 g, 7.22 mmol) was dissolved in a solution of sodium thiosulfate (10 eq.) in water (50 mL) and allowed to stand overnight. The reaction mixture was then cooled with an ice-water bath and chlorine gas passed through the solution at such a rate that the temperature of the mixture did not exceed 10° C. When the reaction appeared complete the mixture was washed with ether. The ether phase was washed with sodium bisulfite, sodium bicarbonate, water, dried and the solvent removed by evaporation to give 1-butanesulfonyl chloride as a clear liquid (880 mg, 78%); ir ν_{max}: 2968 (s), 2939 (m), 2880 (m), 1469 (m), 1373 (vs), 1312 (w), 1237 (m), 1165 (vs), 1100 (w), 1078 (w), 915 (w) cm^{-1}; ^1H nmr δ: 1.01 (t, 3H), 1.56 (m, 2H),

2.02 (m, 2H), 3.70 (t, 2H). The spectra were identical to those of an authentic sample obtained from Eastman Organic.

c) Preparation of 1-Butanesulfonyl Chloride Using Thiourea

The previous experiment was repeated using 12.9 mmol of betylate and 129 mmol of thiourea. The usual workup gave 62% yield of 1-butanesulfonyl chloride.

Reactions of 3-(Alkoxysulfonyl)-N,N,N,-trimethylpropanaminium salts (Alkyl [3]Betylates) in Two Phase Aqueous-Organic Media (General Procedure)

The betylate was dissolved in an organic solvent (typically methylene chloride, chloroform, or benzene). A solution of reactant in an equal amount of water was added and the mixture stirred at a moderate rate. The reaction mixture was worked up by dilution with methylene chloride and water. The organic layer dried with anhydrous magnesium sulfate and evaporated to dryness. If necessary the product was dissolved in benzene and passed through a pad of silica gel.

a) Preparation of N-Butyl Imidazole

Butyl [3]betylate fluorosulfate (371 mg, 1.10 mmol) and imidazole (752 mg, 10 eq.) were dissolved in water (0.5 mL) and chloroform (5 mL) was added. The mixture was stirred for 17 h, the organic phase washed with water, dried and evaporated to give N-butyl imidazole as an oil (115 mg, 84%); ir ν_{max}: 3047 (w), 2968 (s), 2940 (s), 2830 (m),

1510 (s), 1465 (m), 1232 (s), 1111 (m), 1081 (s), 1033 (w), 911 (m), 820 (m) cm^{-1}; ^1H nmr δ: 0.93 (t, 3H), 1.10 (m, 2H), 1.76 (m, 2H), 3.93 (t, 2H), 6.92 (s, 1H), 7.06 (s, 1H), 7.47 (s, 1H). An authentic sample was prepared by the method of von Auwers and Mauss (43). Although both samples were hygroscropic the spectra were identical.

b) Preparation of 1-Methylheptyl Phenyl Thioether

The general procedure for reactions in two phase aqueous-organic media was used. 1-Methylheptyl [3]betylate fluorosulfate (403 mg, 1.03 mmol) was dissolved in chloroform (10 mL) and stirred under nitrogen with a solution made up of thiophenol (1.05 mL, 10 eq.) in water to which sodium hydroxide (400 mg, 10 eq.) had been added. The reaction mixture was stirred for 18 h under nitrogen and worked up to give the product (134 mg, 59%; ir ν_{max}: 2961 (s), 2932 (s), 2860 (s), 1584 (m), 1480 (m), 1439 (m), 1377 (m), 1091 (w), 1068 (w), 1025 (w), cm^{-1}; ^1H nmr δ: 0.88 (t, 3H); 1.27 (d, plus methylene signal , 11H), 1.50 (m, 2H), 3.21 (m, 1H), 7.32 (m, 5H). The spectra were identical to those of an authentic sample prepared by the method of Eliel and Ro (44).

c) Preparation of Hexadecyl Azide

The general method for reactions in two phase aqueous-organic media was used. Hexadecyl [3]betylate fluorosulfate (233 mg, 0.460 mmol) was dissolved in methylene chloride (5 mL) and stirred with a solution of sodium azide (10 eq.) in water for 24 h. Workup gave hexadecyl azide (123 mg, 100%); ir ν_{max}: 2929 (s), 2858 (s), 2100 (s), 1467 (m) cm^{-1}; ^1H nmr δ: 0.87 (t, 3H), 1.24 (s, 26H), 1.57 (m, 2H), 3.22

(t, 2H). The spectra were identical to those of an authentic sample prepared by the method of Leiber et al.(45).

(d) Preparation of Hexadecyl Iodide

The general procedure for reactions in two phase aqueous-organic media was used. Hexadecyl [3]betylate perchlorate (2.53 mg, 0.5 mmol) was dissolved in chloroform (5 mL) and stirred with a solution of sodium iodide (10 eq.) in water for 72 h. Workup gave the product (159 mg, 90%); ir ν_{max}: 2930 (s), 2858 (s), 1466 (m); ^{1}H nmr δ: 0.88 (t, 3H), 1.28 (s, 26H), 1.82 (m, 2H), 3.18 (t, 2H). The spectra were identical to those of an authentic sample prepared by the method of Guyer et al.(46).

e) Preparation of Hexadecyl Thiocyanate

The general procedure for reactions in two phase aqueous-organic media was used. Hexadecyl [3]betylate perchlorate (252 mg, 0.5 mmol) was dissolved in chloroform (6 mL) and stirred with a solution of sodium thiocyanate (10 eq.) in water for 72 h. Workup gave the product (142 mg, 93%); ir ν_{max}: 2931 (s), 2857 (s), 2158 (m), 1467 (m) cm^{-1}; ^{1}H nmr δ: 0.88 (t, 3H), 1.27 (s, 26H), 1.83 (m, 2H), 2.95 (t, 2H). The spectra were identical to those of an authentic sample prepared by the method of Reimschneider and Orlick (47).

f) Preparation of Hexadecyl Phenyl Thioether

The general procedure for the reaction in two phase aqueous-organic media was used. Hexadecyl [3]betylate fluorosulfate (253 mg, 0.5 mmol)

was dissolved in benzene (5 mL) and stirred with a solution of thiophenol (0.52 mL, 10 eq.) and sodium hydroxide (200 mg, 10 eq.) under nitrogen for 18 h. Workup gave the product (159 mg, 95%). Recrystallization from ethanol gave white crystals, mp 48-50° C; ir ν_{max}: 2931 (s), 2858 (s), 1585 (w), 1482 (w), 1470 (w), 1440 (w), 1186 (w), 1150 (m), 1112 (m), 1092 (w), 1028 (w) cm^{-1}; ^1H nmr δ: 0.88 (t, 3H), 1.24 (s, 26H), 2.90 (t, 2H), 7.26 (s, 5H). The spectra were identical to those of an authentic sample prepared by the method of Takahashi et al (48) and a mixed melting point showed no depression.

(g) Preparation of Hexadecyl Cyanide

The general procedure for the reaction in two phase aqueous-organic media was used. Hexadecyl [3]betylate fluorosulfate (253 mg, 0.5 mmol) was dissolved in benzene and stirred with sodium cyanide (10 eq.) in water for 72 h. Workup gave the product (119 mg, 95%); ir ν_{max}: 2931 (s), 2858 (s), 2249 (w), 1468 (m) cm^{-1}; ^1H nmr δ: 0.88 (t, 2H), 1.26 (s, 26H), 1.60 (m, 2H), 2.33 (t, 2H). The spectra were identical with those of an authentic sample prepared by refluxing hexadecyl iodide with sodium cyanide in ethanol.

In a duplicate experiment on a 2 mmol scale of the betylate, a yield of 70% was obtained.

(h) Preparation of Hexadecyl Bromide

The general procedure for reactions in two phase aqueous-organic media was used. Hexadecyl [3]betylate fluorosulfate (252 mg, 0.5 mmol) was dissolved in benzene (5 mL) and stirred with a solution of sodium

bromide (10 eq.) for 48 h. Work up gave the product (146 mg, 96%); ir ν_{max}: 2930 (s), 2858 (s), 1467 (w) cm^{-1}; ^1H nmr showed bands at 0.88 (t, 3H), 1.26 (s, 26H), 1.85 (m, 2H), 3.40 (t, 2H). The spectra were identical with those of an authentic sample prepared by the method of Kamm and Marvel (49).

(i) Preparation of S-(+)-1-Methylheptyl Thiocyanate

The general procedure for reactions in two phase aqueous-organic media was used. R-(-)-1-methylheptyl [3]betylate fluorosulfate prepared from commercial R-(-)-2-octanol (3.45 g, $[\alpha]_D^{21}$ - 9.35°) was dissolved in methylene chloride (50 mL) and stirred with a solution of sodium thiocyanate (58 g, 680 mmol) in water for 15 h. The usual work up gave a product which contained a small amount of the isothiocyanate. This material was detected by the presence of the broad isothiocyanate absorbtion at 2084 cm^{-1} in the infrared spectrum. The product was purified by the method of Cram (29) to give S-(+)-1-Methylheptyl thiocyanate (3.45 g, 75% based on alcohol). The product was purified by short path distillation at 1 torr, $[\alpha]_D^{23}$ + 57.4° (d = 0.919 (24)), $[\alpha]_{546}^{23}$ + 74.4° (d = 0.919), $[\alpha]_D^{21}$ + 73.7° (c 4.93, ethanol), $[\alpha]_{546}^{21}$ + 84.9° (c 4.93, ethanol), $[\alpha]_D^{23}$ + 70.1° (c 4.84, abs. ethanol), $[\alpha]_{546}^{23}$ + 83.6 (c 4.84, abs. ethanol); 2965 (m), 2936 (s), 2877 (m), 2864 (m), 2159 (m), 1457 (w), 1483 (w) cm^{-1}; ^1H nmr δ: 0.89 (t, 3H), 1.35 (s, 8H), 1.52 (d, 3H), 1.71 (m, 2H), 3.28 (m, 1H). The ir and nmr spectra were identical to those of a racemic sample prepared by the method of Cram (29).

(j) Preparation of S-(+)-1-Methylheptyl Azide

The general procedure for reactions in two phase aqueous-organic media was used. R-(-)-1-methylheptyl [3]betylate fluorosulfate prepared from commercial R-(-)-2-octanol (3.45 g, $[\alpha]_D^{21}$ - 9.35°) was dissolved in methylene chloride (50 mL) and stirred with a solution of sodium azide (20 g, 310 mmol) in water for 15 h. The usual work up gave the product as a clear liquid (2.57 g, 85%). The product was purified by short path distillation at 5 torr, $[\alpha]_D^{22}$ + 44.3° (d = 0.8555 (25)), $[\alpha]_{546}^{22}$ + 52.5° (d = 0.8555), ir ν_{max}: 2962 (m), 2938 (s), 2875 (m), 2863 (m), 2105 (s), 1478 (w), 1470 (w), 1381 (w), 1239 (w) cm^{-1}; ^1H nmr 0.90 (t, 3H), 1.22 (s, due to methyl), 1.28 (s, 10H), 3.41 (m, 1H). The ir and nmr spectra were identical to those of a racemic sample prepared from 1-methylheptyl iodide and sodium azide.

(k) Preparation of S-(+)-1-Methylheptyl Iodide

The general procedure for reactions in two phase aqueous-organic media was used. R-(-)-1-methylheptyl [3]betylate fluorosulfate prepared from R-(-)-2-octanol (3.3 g, $[\alpha]_D^{21}$ - 9.35°) was dissolved in methylene chloride (50 ml) and stirred with a solution of sodium iodide (50 g, 330 mmol) in water for 15 h. The usual work up procedure was used except that the crude product was dissolved in pentane and stirred with charcoal and silica gel. Filtration followed by removal of the solvent by evaporation gave a colorless liquid (3.3 g, 53% based on alcohol). The product was purified by distillation $bp_{1.3}$ 51° (lit. (26) $bp_{1.5}$ 54-55°); $[\alpha]_D^{21}$ 43.7°

(d = 1.3219 (26)), $[\alpha]_{546}^{21}$ + 69.3° (d = 1.3219); ir ν_{max}: 2955 (s), 2934 (s), 2878 (s), 2865 (s), 1455 (m), 1378 (m), 1135 (m) cm^{-1}; ^1H nmr δ: 0.90 (t, 3H), 1.32 (s, 8H), 1.47 (m, 2H), 1.92 (d, 3H), 4.20 (m, 2H); ms M^+ calcd.: 240.0375; found: 240.0380. The spectra were identical to those of an authentic sample of S-(+)-1-Methylheptyl iodide prepared by M. Aslam (35).

Reactions of 3-(Alkoxylsulfonyl)-N,N,N-trimethylpropanaminium salts (Alkyl [3]Betylates) and 3-(alkoxysulfonyl)-N,N-dimethylpropanaminium salts (Alkyl [3]Norbetylates) in Refluxing Organic Solvents; Substrate-Reagent Ion-Pair (SRIP) Reactions. General Procedure.

The betylate or norbetylate was refluxed in an organic solvent (usually toluene). As the reaction progressed formation of a precipitate (the insoluble betaine) was observed. After refluxing, the solvent volume was reduced by evaporation to 2-3 mL and the mixture passed through a pad of silica gel in a sintered glass funnel. Benzene was used as the eluant and the final product was obtained by evaporation.

(a) Preparation of Hexadecyl Bromide via a [3]Norbetylate Bromide

Hexadecyl 3-(dimethylamino)propanesulfonate (238 mg, 0.608 mmol) was dissolved in methylene chloride (15 mL) and the solution cooled to 0° C. Hydrogen bromide was bubbled through the solution for 5 min. Evaporation of the solvent gave a residue which was refluxed in toluene (25 mL) for 2 h and worked up as described in the general procedure for SRIP reactions to give the product (128 mg, 69%).

(b) Preparation of Hexadecyl Picryl Ether

The general procedure for SRIP reactions was used. Hexadecyl [3]betylate picrate was refluxed in toluene (30 mL) for 3 h. Work up gave the product (296 mg, 93%). Recrystallization from ethanol gave white crystals, mp 63-64° C; ir ν_{max}: 2931 (m), 2858 (w), 1607 (w), 1550 (s), 1347 (s) cm^{-1}; ^1H nmr δ: 0.88 (t, 3H), 1.27 (s, 26H), 1.84 (m, 2H), 4.26 (t, 2H), 8.87 (s, 2H). Anal. calcd. for $C_{22}H_{35}N_3O_7$: C 58.26, H 7.78, N 9.27, O 24.69; found: C 58.34, H 7.90, N 9.09.

In a duplicate experiment the betylate was refluxed in benzene with a 75% recovery of starting material.

(c) Preparation of Hexadecyl Sulfate

The general procedure for SRIP reactions was used. Hexadecyl [3]betylate fluorosulfate (187 mg, 0.370 mmol) was refluxed in toluene (20 mL) for 4.5 h. Work up gave the product (87 gm, 86%); ir ν_{max}: 2928 (s), 2857 (s), 1478 (m), 1399 (m), 1382 (m), 1195 (s) cm^{-1}; ^1H nmr δ: 0.87 (t, 6H), 1.24 (s, 52 H), 1.71 (m, 4H), 4.23 (t, 4H). The spectra were identical to those of an authentic sample prepared by Dr. S.M. Loosmore (19).

(d) The Refluxing of Hexadecyl [3]Betylate Methylsulfate in Toluene

The general procedure for SRIP reactions was used. Hexadecyl [3]betylate methylsulfate (268 mg, 0.519 mmol) was refluxed in toluene for 2 h. Work up gave a mixture of hexadecyl sulfate (59%) and

hexadecyl methylsulfate (29%) as estimated by integration of the ^{1}H nmr spectrum.

(e) Preparation of Hexadecyl Perchlorate

The general procedure for SRIP reactions was used. Hexadecyl [3]betylate perchlorate (194 mg, 0.388 mmol) was refluxed in toluene for 4 h. Work up gave the product (39 mg, 32%); ir (CCl_4; Beckmann Acculab 4, uncalibrated) ν_{max}: 2950 (s), 2825 (s), 1450 (m), 1250 (s), 1215 (s), 1020 (m) cm^{-1}; ^{1}H nmr (CCl_4) δ: 0.89 (t, 3H), 1.26 (s, 26H), 1.83 (m, 2H), 4.55 (t, 2H). The spectra were identical to those of an authentic sample prepared by the method of Baum and Beard (80).

(f) Preparation of Hexadecyl Thiocyanate

A sample of hexadecyl [3]betylate perchlorate (0.5 mmol) in chloroform (10 mL) was stirred with a saturated aqueous solution of sodium thiocyanate for 2 h. The organic phase was separated from the aqueous phase using a separatory funnel and refluxed for 18 h. The usual work up gave a 92% yield of hexadecyl thiocyanate, (see p. 208).

(g) Preparation of Hexadecyl Chloride from Hexadecyl [3]Betylate Chloride Obtained using an Ion Exchange Resin

A sample of Rexyn 201 (chloride-sulfate form) was washed with concentrated aqueous potassium chloride until the wash solution gave a negative test for sulfate ion with aqueous barium chloride. The resin

was then washed with water until the wash tested negative for chloride ion with aqueous silver nitrate. The solvent was replaced with methanol prior to use.

Hexadecyl [3]betylate fluorosulfate (0.62 mmol) in methanol was passed through a column containing the chloride form of the resin (30 meq). The eluant was evaporated to dryness and the material remaining was refluxed in toluene for 2 h. The usual work up gave the product (157 mg, 97%); ir ν_{max}: 2926 (s), 2847 (s), 1467 (m) cm^{-1}; ^1H nmr δ: 0.87 (t, 3H), 1.25 (s, 26H), 1.74 (m, 2H), 3.50 (t, 2H). The spectra were identical to those of an authentic sample prepared by the method of Norris and Taylor (51).

During a repetition of this experiment the precipitate formed during refluxing of the betylate chloride was collected by filtration before work up. This precipitate was identified by comparison with an authentic sample prepared by the method of Blumbergs et al. (12) from propanesultone and trimethylamine.

(h) Preparation of Hexadecyl Acetate from Hexadecyl [3]Betylate Fluorosulfate using an Ion Exchange Resin

Rexyn 201 (chloride-sulfate form; 100 mL, 100 meq) was washed with aqueous sodium hydroxide until the eluant tested negative for chloride and sulfate. The column was rinsed with distilled water until the eluant was no longer basic to pH paper. The resulting hydroxide resin was treated with dilute acetic acid (300 meq) and washed with water to neutrality. The water was replaced with methanol prior to use. It was observed that the acetate resin could be stored

dry and used several times.

Hexadecyl [3]betylate fluorosulfate (2,00 g, 3.97 mmol) in methanol was passed through a column containing the acetate resin. After evaporation of the solvent the residue was refluxed in benzene (30 mL) for 4 h. The usual work up gave the produce as a clear liquid (1.03 g, 91%); ir ν_{max}: 2930 (s), 2868 (m), 1732 (m), 1470 (w), 1368 (w), 1244 (m), 1040 (w) cm^{-1}; ^1H nmr δ: 0.88 (t, 3H), 1.27 (s, 26H), 1.62 (m, 2H), 2.05 (s, 3H), 4.05 (t, 2H). The spectra were identical to those of an authentic sample prepared hexadecyl alcohol and acetic anhydride.

(i) Preparation of Hexadecyl Fluoride from Hexadecyl [3]Betylate Fluorosulfate using an Ion Exchange Resin

A sample of the hydroxide resin (110 ml, 115 meq) prepared as described in the preparation of hexadecyl acetate in a column was treated with a dilute solution of hydrofluoric acid (500 mL, 1.7 M). The column was washed with distilled water and the solvent replaced with methanol.

Hexadecyl [3]betylate fluorosulfate (2.02 g, 4.00 mmol) in methanol was passed through the resin. After removal of the methanol by evaporation the residue was refluxed in toluene (50 mL) over molecular seives for 72 h. The usual work up, except for the use of basic alumina with petroleum ether (bp 30-60° C) instead of silica gel with benzene, gave the product as a clear liquid (654 mg, 67%). Repeated short path distillation gave an analytical sample ($bp_{0.18}$ 130° C); ir ν_{max}: 2928 (s), 2857 (s), 1465 (w), 1042 (w), 995 (w) cm^{-1};

^{1}H nmr δ: 0.88 (t, 3H), 1.27 (s, 2H), 4.20 (t, 1H), 4.68 (t, 1H); ^{19}F nmr δ: 218.7 (apparent heptet). Anal. calcd. for $C_{16}H_{33}F$: C 78.62, H 13.61; found: C 78.49, H 13.83.

Reactions of 3-(Alkoxysulfonyl)-N,N,N,-trimethylpropanaminium salts (Alkyl [3]Betylates) in One Phase Organic Media

(a) Preparation of N-Ethyl Phthalimide

Ethyl[3]betylate fluorosulfate (1.01 g, 3.28 mmol) was dissolved in dimethylformamide (15 mL) and potassium phthalimide (0.622 g, 1.05 eq.) was added. The suspension was stirred for 6 h at room temperature, diluted with water and extracted with methyl chloride. The organic phase was washed with dilute hydroxide, water, dried and evaporated to give the product (0.433 g, 76%). Recrystallization from ethanol gave white crystals, mp 74-75° C, lit 77° C ir ν_{max}: 1775 (m), 1711 (s), 1499 (s), 1354 (m), 1035 (m) cm^{-1}; ^{1}H nmr δ: 1.28 (t, 3H), 3.76 (q, 2H), 7.80 (m, 4H). The spectra were identical to those of an authentic sample prepared under the same conditions from ethyl bromide and a mixed melting point showed no depression.

(b) Preparation of Butyl Cyclopropanesulfonate

Butyl [3]betylate fluorosulfate (345 mg, 1.02 mmol) was dissolved in dry THF (distilled from LAH) at -78° under nitrogen. Butyllithium solution (0.5mL, 1.2 eq.) was added dropwise via a syringe and the mixture was stirred for 2 h, washed with brine, dried and the solvent removed by evaporation. The crude product was dissolved in

benzene and passed through a pad of silica gel. The solvent was removed by evaporation to give a liquid (138 mg, 76%).

An analytical sample was prepared by repeated bulb to bulb distillation at 0.2 torr; ir ν_{max}: 3067 (w), 2969 (m), 2940 (m), 2880 (w), 1469 (w); 1384 (w), 1356 (s), 1315 (m), 1194 (w), 1173 (s), 1074 (w), 1048 (m), 1029 (w), 1017 (w), 991 (w), 948 (s), 889 (s), 833 (m), 799 (m) cm^{-1}; ^1H nmr δ: 0.8 - 1.9 (complex pattern, 11H) 2.49 (m, 1H), 4.27 (t, 2H); ^{13}C nmr δ: 5.193 (m), 13.168 (q), 18.413 (t), 27.001 (d), 30.905 (t), 70.055 (t). Anal. calcd. for $C_7H_{14}O_3S$: C 47.17, H 7.92, S 17.99; found: C 47.29, H 8.08, S 17.78.

(c) Preparation of Hexadecyl Ethyl Ether

Sodium metal (300 mg, 13 mmol) was stirred in absolute ethanol (5 mL) until completely reacted. Hexadecyl [3]betylate perchlorate (252 mg, 0.5 mmol) was added and the mixture stirred for 48 h. The reaction mixture was diluted with methylene chloride and water, the organic layer was dried and the solvent removed by evaporation. Short path distillation gave the product (137 mg, 100%); ir ν_{max}: 2929 (s), 2857 (s), 1468 (w), 1380 (w), 1356 (w), 1108 (m) cm^{-1}; ^1H nmr δ: 0.88 (t, 3H), 1.19 (t, partially obscured, 3H), 1.27 (s, 26H), 3.40 (t, 2H), 3.46 (q, 2H). The spectra were identical to those of a sample prepared from hexadecyl bromide and sodium ethoxide.

(d) Preparation of Hexadecylmethylamine Hydrochloride

To a stirred solution of hexadecyl [3]betylate fluorosulfate (1.01 g, 2 mmol) in dimethoxyethane (50 mL) an aqueous solution of methylamine

(40%, 2 mL) was added. The resulting murky solution was stirred for 24 h, diluted with water and extracted with methylene chloride. The organic phase was dried, the solvent removed by evaporation, and the residue dissolved in ether. Gaseous hydrogen chloride was bubbled through the ether solution until precipitation appeared complete. After removal of solvent by evaporation the product was recrystallized from ethyl acetate to give white crystals (0.35 g, 60%); mp 165-167° C, literature mp 169-170° C (52); ir ν_{max}: 2959 (m), 2930 (s), 2907 (m), 2750 (m), 2445 (w), 1592 (w), 1466 (m) cm^{-1}; ^1H nmr 0.87 (t, 3H), 1.25 (s, 26H), 1.95 (m, 2H), 2.67 (s, 3H), 2.90 (m, 2H).

NMR Determination of the Rates of Hydrolysis of 3-(Ethoxysulfonyl)-N,N,N-trimethylpropanaminium Fluorosulfate and Perchlorate (Ethyl [3]Betylate Fluorosulfate and Perchlorate) in Deuterium Oxide

A 50 mg sample (0.16 mmol) of the betylate was dissolved in deuterium oxide and placed into an nmr tube. The progress of the reaction was followed using a T-60 nmr spectrometer at a probe temperature of 37° C by measuring the heights of the center peak of the ethyl triplet of the betylate and of the ethanol produced by the hydrolysis reaction. The percentage of betylate remaining at any time during the reaction was then calculated by taking the ratio of the betylate peak height to the sum of the peak heights of the betylate and the product. The kinetic data are shown in Table 3.7. The natural log of the percentage betylate remaining versus time in minutes was plotted to give a straight line as shown in Figure 3.4 for the hydrolysis of ethyl [3]betylate perchlorate. A least squares analysis was used

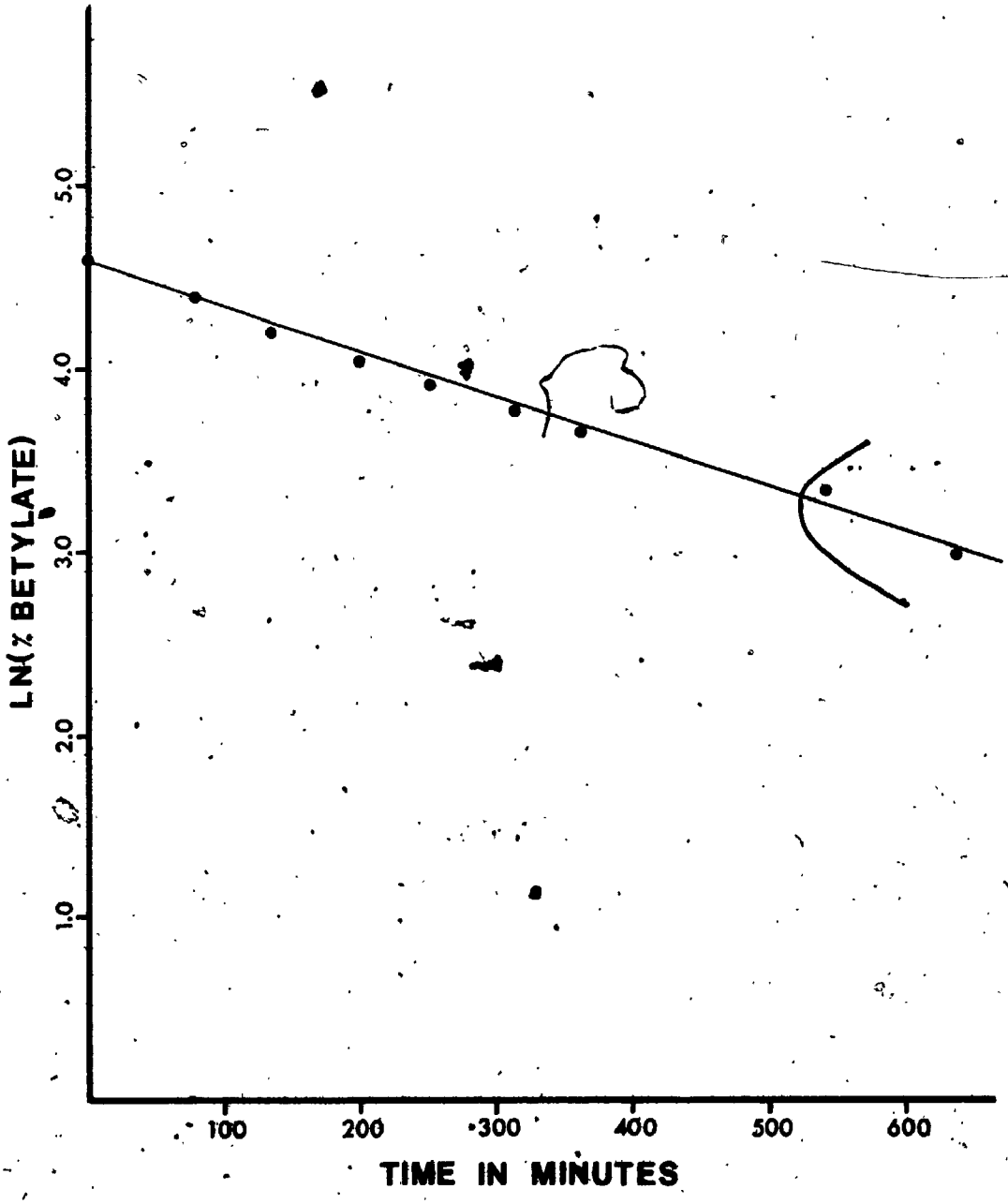
Table 3.7. Kinetic Data for Hydrolysis of Ethyl[3]Betylates in Deuterium Oxide

Ethyl[3]betylate fluorosulfate			Ethyl[3]betylate perchlorate		
time in minutes	peak heights in mm. betylates	product	time in minutes	peak heights in mm. betylate	product
0	88	7	0	125	0
10	82	9	78	105	25
29	80	14	138	95	42
40	78	16	203	73	49
55	74	18	253	60	62
85	69	23	318	56	72
110	63	26	368	51	82
136	60	30	543	33	81
171	67	41	638	23	94
209	71	50			
239	68	54			
665	25	87			
699	24	93			
704	24	91			
733	23	100			
738	24	97			
788	27	111			

rate constant : 3.4×10^{-5} s^{-1}
correlation coefficient: -0.999

rate constant: 4.1×10^{-5} s^{-1}
correlation coefficient: -0.995

Figure 3.4. First Order Plot for the Deuterolysis of Ethyl [3]Betylate Perchlorate.



to determine the slope of the line which gave the best fit to the data. The values of the first order rate constants in reciprocal seconds obtained from the slopes of the lines for the two hydrolyses are shown in Table 3.7 along with the correlation coefficients obtained. It should be noted that the reaction solvent was acidic to pH paper (~3) after completion of the nmr experiment.

NMR Determination of the Rate of Reaction of 3-(Ethoxysulfonyl)-N,N,N,trimethylpropanaminium Fluorosulfate (Ethyl [3]Betylate Fluorosulfate) with Thiosulfate in Deuterium Oxide.

To a sample of the betylate (50.4 mg) in deuterium oxide (0.25 mL) a drop of deuteroxide was added to ensure that the pH of the reaction solution would remain alkaline during the kinetic run. To this solution an equal volume of standardized sodium thiosulfate (0.6708 M) was added and the time of addition taken as time zero for the kinetic run. The solution was transferred into an nmr tube which was placed into the probe of a Varian XL100 spectrometer. The probe temperature was controlled to 25.1 ± 0.2° C during the kinetic run. The progress of the reaction was followed by measuring the heights of the center peak of the ethyl triplet of the betylate and of the product, ethyl thiosulphate. The kinetic data are shown in Table 3.8.

The concentration of betylate at any time was calculated by multiplying the initial concentration of the betylate (0.3258 M) by the ratio of the peak height to the sum of the betylate peak height and the product peak height. The concentration of the thiosulfate at any time was calculated in an analogous manner. The natural log of the

Table 3.8 Kinetic Data for the Reaction of Ethyl [3]Betylate Fluorosulfate with Thiosulfate in Deuterium Oxide.

time in minutes	peak heights in mm. betylate	product	time in minutes	peak heights in mm. betylate	product
0.75	218	28	30.15	106	135
1.58	208	35	31.08	106	135
2.58	202	43	32.08	106	145
3.58	196	48	33.08	106	146
4.50	193	57	34.08	101	138
5.50	186	62	35.22	102	145
6.55	179	65	36.25	103	154
7.55	179	70	37.16	100	150
8.47	167	75	38.15	101	158
9.47	153	78	39.16	97	157
10.47	161	86	40.25	95	156
11.45	159	88	41.17	94	156
12.50	154	99	42.15	94	166
13.37	160	98	43.08	94	163
14.42	146	100	44.12	90	158
15.45	143	105	45.25	91	163
16.50	140	110	46.17	87	154
17.42	137	109	47.18	84	165
18.35	136	111	48.25	86	161
19.33	131	117	49.33	85	168
20.33	139	119	50.50	82	169
21.28	129	122	51.33	83	169
22.25	129	126	57.25	84	170
23.17	124	125	63.00	79	176
24.22	120	130	68.75	73	182
25.25	122	136	79.83	66	190
26.25	116	129	83.33	59	192
27.17	116	136	100.33	54	192
28.12	114	140	117.33	49	195
29.08	112	137	135.33	49	208

rate constant: $1.6 \times 10^{-3} M^{-1} s^{-1}$
correlation coefficient; 0.992

ratio of the betylate concentration to thiosulfate concentration versus time was plotted to give a straight line as shown in Figure 3.5. A least squares analysis was used to determine the slope of the line which gave the best fit to the data. The value of the second order rate constant obtained from the slope is shown in Table 3.8 along with the correlation coefficient obtained.

Figure 3.5. Second Order Plot for the Reaction of Ethyl [3]Betylate Fluorosulfate with Thiosulfate in Deuterium Oxide.

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APPENDICES

Appendix 1

The derivation of the algebraic expressions which describe the reaction scheme of Figure 1.4 (see also Figure A1.1) where the concentration of active hydrogen is assumed to be zero is given in this appendix. The following definitions and relationships were used:

$$x = k_4/k_{12}$$

$$d = k_{10}/k_6$$

$$a = k_7/k_9$$

$$I = \frac{1}{H} = \frac{k_4}{k_{11}}$$

$$u = k_3/k_1$$

$$v = k_2/k_1$$

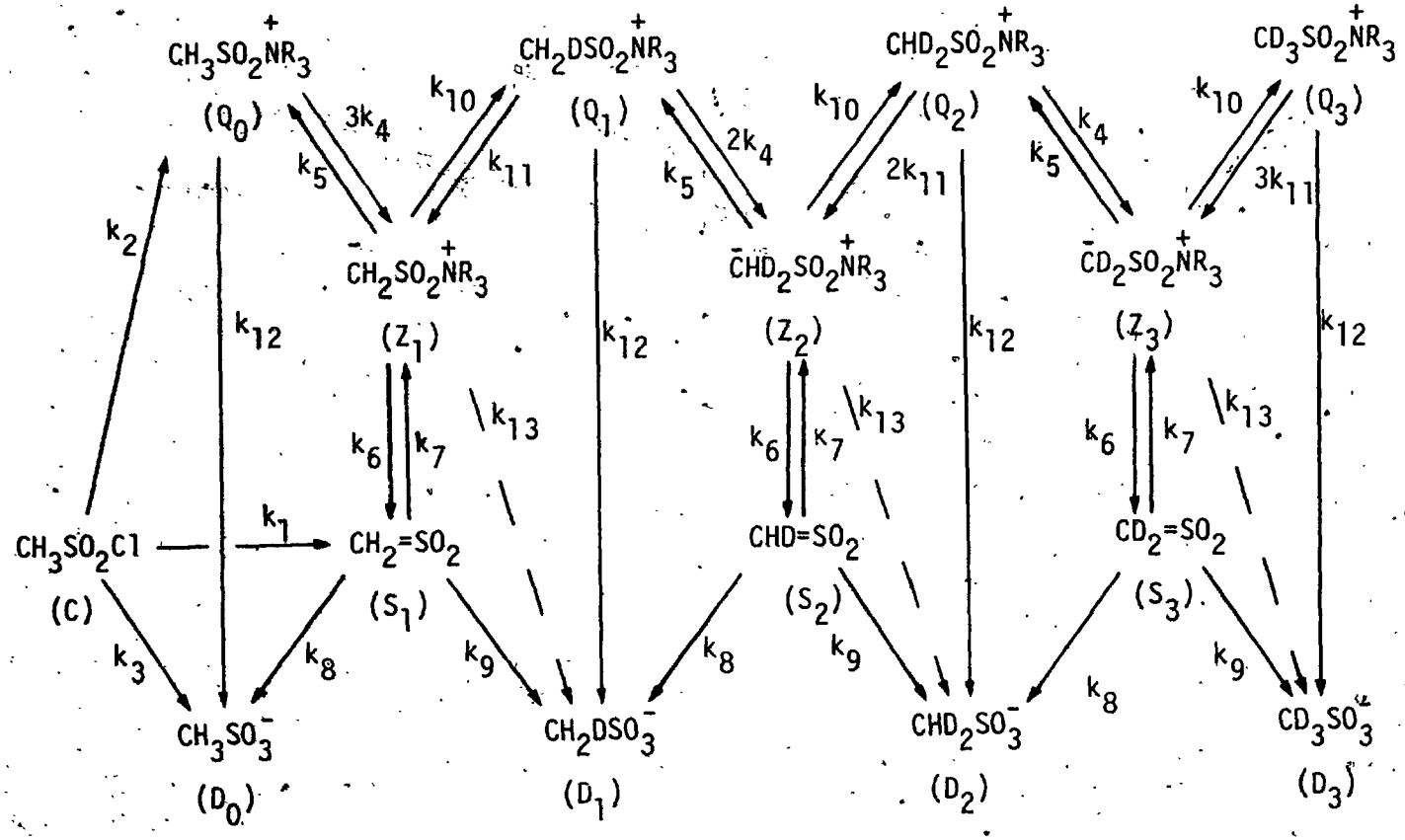
and $$y = k_{10}/k_{13} = d(a+1)$$

The assumption that there is no active hydrogen present requires that the rate constants k_5 and k_8 equal zero. The following examples illustrate the symbolism which was used: $D_3^{k_{12}}$ was the term used to represent the amount of trideuterated methanesulfonate anion produced via the pathway labelled with the rate constant k_{12} in Figure A1.1; $[D_3^{k_{12}}]$ represents the concentration of this species; and D_3^T represents the total amount of trideuterated methanesulfonate formed by all possible routes.

A1.1 Derivation of the Expressions for the Reaction with Trialkyl(methylsulfonyl)ammonium fluorosulfates as the Starting Material.

The rate constant k_{13} (see Scheme A1.1) can be expressed in terms

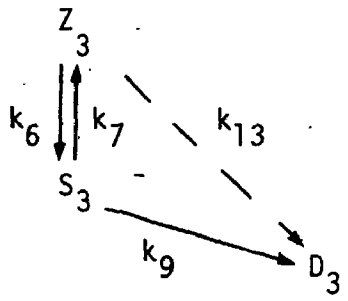
Figure A1.1 Proposed Multiexchange Mechanism for the Reactions of Trialkyl(methylsulfonyl)ammonium Fluorosulfonate Salts and Methanesulfonyl Chloride[a,b].



a: rate constants are pseudo-first order on a per hydrogen basis.

b: the rate constants k_5 and k_8 are equal to zero for this appendix.

Scheme A1.1



of k_6, k_7 and k_9. Using the steady state approximation

$$\frac{d}{dt}[S_3] = 0$$

and $$\frac{d}{dt}[S_3] = k_6[Z_3] - k_7[S_3] - k_9[S_3]$$

Thus, $$k_6[Z_3] = (k_7 + k_9)[S_3]$$

$$[S_3] = \frac{k_6}{k_7 + k_9}[Z_3]$$

Since $$\frac{d}{dt} D_3^{k_9} = k_{13}[Z_3]$$

and $$\frac{d}{dt} D_3^{k_9} = k_9[S_3],$$

$$k_{13} = \frac{k_6}{k_7 + k_9} k_9$$

The ratio of the rate constants for formation of the methylsulfonyl-ammonium cation from the zwitterion vs formation of product from the

zwitterion was defined as: $y = k_{10}/k_{13}$. Substitution for k_{13} gave:

$$y = \frac{k_{10}(k_7 + k_9)}{k_6 \; k_9}$$

or $$y = d(a+1)$$

The number of Q_3 formed from the zwitterion Z_3, $Q_3^{k_{10}}$, is a fraction (k_{10}/k_{13}) of the number of D_3 formed from the zwitterion, Z_3, so that

$$\frac{k_{10}}{k_{13}} D_3^{k_{13}} = Q_3^{k_{10}}$$

or $$D_3^{k_{13}} = \frac{k_{13}}{k_{10}} Q_3^{k_{10}} \qquad (1)$$

Since Z_3 is the only source of Q_3, $Q_3^{k_{10}}$ can be written as Q_3^T.

The total amount of D_3 formed is given by

$$D_3^T = D_3^{k_{12}} + D_3^{k_{13}} \qquad (2)$$

Substitution of equation 1 into equation 2 gives:

$$D_3^T = D_3^{k_{12}} + \frac{k_{13}}{k_{10}} Q_3^T$$

$$= D_3^{k_{12}} + \frac{1}{y} (Q_3^T) \qquad (3)$$

Since the only materials remaining at the end of the reaction are D_0, D_1, D_2 and D_3, preservation of mass balance requires that the amount of each intermediate formed must be equal to the amount of each intermediate consumed, ie. for Q_3^T.

$$Q_3^T = Z_3^{k_{11}} + D_3^{k_{12}}$$

and so $$D_3^T = D_3^{k_{12}} + \frac{1}{y}(Z_3^{k_{11}} + D_3^{k_{12}})$$

The ratio of $Z_3^{k_{11}}$ to $D_3^{k_{12}}$ is given by

$$\frac{Z_3^{k_{11}}}{D_3^{k_{12}}} = \frac{3k_{11}}{k_{12}}$$

so that $$Z_3^{k_{11}} = \frac{3k_{11}}{k_{12}} D_3^{k_{12}}$$

and $$D_3^T = D_3^{k_{12}} + \frac{1}{y}(\frac{3k_{11}}{k_{12}} D_3^{k_{12}} + D_3^{k_{12}})$$

Substitution of a constant m for $D_3^{k_{12}}$ and $\frac{3x}{I}$ for $\frac{3k_{11}}{k_{12}}$ results in the following expression for the total amount of trideuterated product formed during the multiexchange reaction:

$$D_3^T = m(1 + \frac{1}{y} + \frac{3x}{yI}) \qquad (4)$$

Using the same approach the expression for the dideuterated product was derived as follows:

$$D_2^T = D_2^{k_{12}} + D_2^{k_{13}}$$

$$= \frac{k_{12}}{k_4} Z_3^{k_4} + \frac{k_{13}}{k_{10}} Q_2^{k_{10}}$$

$$= \frac{k_{12}}{k_4} Z_3^{k_4} + \frac{k_{13}}{k_{10}} Q_2^T$$

With $k_5 = 0$, $Z_3^{k_4}$ becomes equal to D_3^T and

$$Q_2^T = \left(\frac{k_4 + k_{12} + 2k_{11}}{k_4}\right) Z_3^{k_4}$$

$$= \left(\frac{k_4 + k_{12} + 2k_{11}}{k_4}\right) D_3^T$$

After substutition

$$D_2^T = \frac{k_{12}}{k_4} D_3^T + \frac{k_3}{k_{10}} \left(\frac{k_4 + k_{12} + 2k_{11}}{k_4}\right) D_3^T$$

$$D_2^T = \left(\frac{1}{x} + \frac{1}{y} + \frac{1}{xy} + \frac{2}{yI}\right) D_3^T$$

For D_1^T:

$$D_1^T = D_1^{k_{12}} + D_1^{k_{13}}$$

$$= \frac{k_{12}}{2k_4} Z_2^{k_4} + \frac{k_{13}}{k_{10}} Q_1^{k_{10}}$$

As before: $Z_2^{k_4} = D_2^T + D_3^T$ and

$$Q_1^{k_{10}} = Q_1^T$$

$$Q_1^T = \left(\frac{2k_4 + k_{12} + k_{11}}{2k_4}\right)(D_2^T + D_3^T)$$

Substitution gives:

$$D_1^T = \frac{k_{12}}{2k_4} (D_2^T + D_3^T) + \frac{k_{13}}{k_{10}} \left(\frac{2k_4 + k_{12} + k_{11}}{2k_4}\right)(D_2^T + D_3^T)$$

$$D_1^T = \left(\frac{1}{2x} + \frac{1}{y} + \frac{1}{2xy} + \frac{1}{2yI}\right)(D_2^T + D_3^T) \qquad (5)$$

For D_0^T:

$$D_0^T = \frac{k_{12}}{3k_4} Z_1^{k_4}$$

$$D_0^T = \frac{1}{3x} (D_1^T + D_2^T + D_3^T) \qquad (6)$$

A1.2. Derivation of the Expressions for the Multiexchange Reaction with Methanesulfonyl Chloride as the Starting Material:

By inspection of the mechanistic scheme the equations for D_3^T and D_2^T for the reaction of the sulfonyl chloride must be the same as those derived in part 1.

The derivation of the expressions for D_1^T and D_0^T was as follows:

$$D_1^T = D_1^{k_{12}} + D_1^{k_9}$$

$$= \frac{k_{12}}{2k_4} Z_2^{k_4} + D_1^{k_9}$$

$$= \frac{1}{2x} (D_2^T + D_3^T) + D_1^{k_9} \qquad (7)$$

Since the sulfene, S_1, can be formed from the sulfonyl chloride (C) as well as from the zwitterion (Z_1), $D_1^{k_9}$ was reevaluated:

$$D_1^{k_9} = \frac{k_9}{k_7} Z_1^{k_7}$$

$$= \frac{1}{a} Z_1^{k_7} \qquad (8)$$

The preservation of mass balance requires that

$$Z_1^{k_7} + Z_1^{k_{11}} + Z_1^{k_4} = S_1^{k_6} + Q_1^{k_{10}}$$

or
$$Z_1^{k_7} = S_1^{k_6} + Q_1^T - Z_1^{k_{11}} - Z_1^{k_4} \qquad (9)$$

Evaluation of the first three terms on the right hand side of eqn. 9 was straightforward:

$$S_1^{k_6} = \frac{k_6}{k_{10}} Q_1^T$$

$$= \left(\frac{1}{d} + \frac{1}{2dx} + \frac{T}{2dI}\right)(D_2^T + D_3^T) \qquad (10)$$

$$Q_1^T = \frac{2k_4 + k_{12} + k_{11}}{2k_4} (D_2^T + D_3^T)$$

$$= \left(1 + \frac{1}{2x} + \frac{1}{2I}\right)(D_2^T + D_3^T) \qquad (11)$$

$$Z_1^{k_{11}} = \frac{k_{11}}{2k_4} (D_2^T + D_3^T)$$

$$= \frac{1}{2I} (D_2^T + D_3^T) \qquad (12)$$

The expression for $Z_1^{k_4}$ is more complex. Starting from the expressions:

$$Q_0^{k_2} = \frac{k_2}{k_1} S_1^{k_1}$$

and
$$D_0^{k_{12}} + Z_1^{k_4} = Q_0^{k_2}$$

one obtains:

$$D_0^{k_{12}} = Q_o^{k_2} - Z_1^{k_4}$$

$$= \frac{k_2}{k_1} S_1^{k_1} - Z_1^{k_4}$$

$$= vS_1^{k_1} - Z_1^{k_4}$$

Since $Z_1^{k_4} = \frac{3k_4}{k_{12}} D_0^{k_{12}}$ substitution gives

$$Z_1^{k_4} = 3x(vS_1^{k_1} - Z_1^{k_4})$$

$$Z_1^{k_4} + 3xZ_1^{k_4} = 3xvS_1^{k_1}$$

$$Z_1^{k_4} = \frac{3xv}{3x+1} S_1^{k_1} \qquad (13)$$

From the mass balance relationship for S_1:

$$S_1^{k_1} = D_1^{k_9} + Z_1^{k_7} - S_1^{k_6}$$

Since $$Z_1^{k_7} = \frac{k_7}{k_9} D_1^{k_9}$$

$$= a D_1^{k_9},$$

$$S_1^{k_1} = (a+1)D_1^{k_9} - S_1^{k_6} \qquad (14)$$

$D_1^{k_9}$ was evaluated as follows:

$$D_1^T = D_1^{k_9} + D_1^{k_{12}}$$

$$D_1^{k_9} = D_1^T - D_1^{k_{12}}$$

$$D_1^{k_9} = D_1^T - \frac{1}{2x}(D_2^T + D_3^T) \qquad (15)$$

Substitution of $D_1^{k_9}$ into eqn. 14 and subsequent substitution of $S_1^{k_1}$ into eqn. 13 gave

$$Z_1^{k_4} = \frac{3xv}{3x+1}\{(a+1)(D_1^T - \frac{1}{2x}(D_2^T + D_3^T)) - S_1^{k_6}\} \qquad (16)$$

The expression for $Z_1^{k_7}$ was obtained by substitution of eqns. 10, 11, 12 and 16 into 9.

$$Z_1^{k_7} = (\frac{1}{d} + \frac{1}{2dx} + \frac{1}{2dI} + 1 + \frac{1}{2x})(D_2^T + D_3^T)$$

$$- \frac{3xv}{3x+1}[(a+1)(D_1^T - \frac{1}{2x}(D_2^T + D_3^T)) - (\frac{1}{d} + \frac{1}{2dx} + \frac{1}{2dI})(D_2^T + D_3^T)] \qquad (17)$$

Substitution of $Z_1^{k_7}$ into equation 8 followed by substitution of $D_1^{k_9}$ into equation 7 gave the expression for D_1^T:

$$D_1^T = (\frac{1}{2x} + \frac{1}{ad} + \frac{1}{2adx} + \frac{1}{2adI} + \frac{1}{a} + \frac{1}{2ax})(D_2^T + D_3^T)$$

$$- \frac{1}{a}\frac{3xv}{3x+1}[(a+1)(D_1^T - \frac{1}{2x}(D_2^T + D_3^T)) - (\frac{1}{d} + \frac{1}{2dx} + \frac{1}{2dI})(D_2^T + D_3^T)] \qquad (18)$$

Rearrangement led to the preferred form where D_1^T was found on the left hand side only:

$$D_1^T = \frac{(\frac{1}{2x} + \frac{1}{ad} + \frac{1}{2adx} + \frac{1}{2adI} + \frac{1}{a} + \frac{1}{2ax})D_2^T + D_3^T)}{(1 + \frac{a+1}{a}\frac{3xv}{3x+1})}$$

$$+ \frac{(\frac{a+1}{2a}\frac{3v}{3x+1} + (\frac{3xv}{3x+1})(\frac{1}{ad} + \frac{1}{2adx} + \frac{1}{2adI})(D_2^T + D_3^T)}{(1 + \frac{a+1}{a}\frac{3xv}{3x+1})}$$

For D_0^T:

$$D_0^T = D_0^{k_{12}} + D_0^{k_3}$$

$$= \frac{k_{12}}{3k_4} Z_1^{k_4} + \frac{k_3}{k_1} S_1^{k_1}$$

$$= \frac{1}{3x} Z_1^{k_4} + u S_1^{k_1}$$

Using equations 14, 15, and 16 as above gave

$$D_0^T = \frac{1}{3x}\frac{3xv}{3x+1}[(a+1)(D_1^T - \frac{1}{2x}(D_2^T + D_3^T)) - S_1^{k_6}]$$

$$+ u[(a+1)(D_1^T - \frac{1}{2x}(D_2^T + D_3^T)) - S_1^{k_6}]$$

Rearrangement and substitution for $S_1^{k_6}$ gave the expression for D_0^T:

$$D_0^T = (u + \frac{v}{3x+1})[(a+1)(D_1^T - \frac{1}{2x}(D_2^T + D_3^T)) - (\frac{1}{d} + \frac{1}{2dx} + \frac{1}{2dI})(D_2^T + D_3^T)] \quad (20)$$

Appendix 2

The computer program and the methodology which was used for the estimation of the parameters necessary to describe the multiexchange reaction are described in this appendix. The program, entitled FINDK, was executed on a CYBER 170/835 in the FORTRAN IV language. A program listing appears at the end of this appendix.

A2.1 Definitions and General Plan

In the program the definitions of x, d, a, I, H, u, v and y are those of Appendix 1. In addition the following definitions and conventions were used in FINDK:

1. E is the vector which contains the experimental results. The percent nondeuterated product from the reaction of the methylsulfonylammonium salt was stored in the first element, and the percent mono, di, and trideuterated in the second, third and fourth elements. The percent nondeuterated product from the sulfonyl chloride was stored in the fifth element followed by the percent mono, di and trideuterated product in the sixth, seventh and eighth elements.
2. YOO and YO8 are the initial lower and upper values of y, respectively.
3. HOO and HO8 are the initial upper and lower values of H, respectively.
4. W1 is the ratio of active deuterium to hydrogen for the reaction of the sulfonylammonium salts.
5. W2 is the analogous ratio for methanesulfonyl chloride.

6. T1 is the time step used in MULTI2 in arbitrary units.
7. R is the total simulation time used in subroutine MULTI2 in arbitrary units.
8. UU is the ratio u (k_3/k_1).
9. UTE is a constant and used in subroutine UV (see below) to control the value of u (UU in FINDK). Although u was normally calculated in subroutine UV its value could be held to the input value if UTE ≠ 100.0.
10. N is an eight membered vector which contains the normalized experimental results (see the discussion of FINDK).
11. CX is a test constant. If CX was input as equal to 1.0 the original input value of x was used throughout the program. Otherwise x was calculated using the percentage of nondeuterated product stored in E(1).

As described in appendix I the algebraic expressions that predict the relative amounts of the deuterated products were based on the assumption that there was no active hydrogen present during the multiexchange reaction. The general approach for finding a solution of the multiexchange system that could incorporate the presence of active hydrogen consisted of the following steps:

1. Assume a value for k_4/k_{12} (x) and k_2/k_1 (v).
2. Assign a range of values for k_{10}/k_{13} (y) and k_{11}/k_4 (H). For some runs of the computer simulation a particular value of k_{11}/k_4 was chosen by setting the upper and lower limit to this parameter to the same value.
3. Assign a particular ratio of active deuterium to hydrogen for the reaction of the salt (W1) and of the sulfonyl chloride (W2)

that one wishes to test for the effect on the fit of predicted (M) to experimental (E) data.

4. Using x and v find the pair of values of k_{10}/k_{13} and k_{11}/k_4 that produce a calculated labelling pattern closest to the experimental one. During this calculation y is broken down into a and d. Also a value of u is calculated.
5. Using x, v, u, a, H and d with the assumption that k_5/k_{10} equals k_{11}/k_4 (H) and the assumed ratios of active deuterium to hydrogen define a set of 12 relative rate constants (k_1 to k_{12}).
6. Calculate the product distribution expected for the rate constants from step 5.
7. Compare the calculated product distribution with the experimental and based on this comparison, adjust the experimental results to the values one would have expected if there was no active hydrogen present during the reactions.
8. Using the adjusted experimental values go back to step 1 and repeat the sequence of steps until no significant further improvement on the fit between calculated and experimental results is found.

In this appendix the sequence of steps 1 to 6 will be referred to as an estimation cycle.

The remainder of this appendix describes in greater detail the execution of FINDK along with any appropriate derivations and the results of the necessary control computing.

A2.2. The Main Program FINDK

The main program, FINDK, was used to control the use of the listed subroutines, to provide the necessary parameters and to stop the simulation at the appropriate time. The inputs were the experimental values (E) to six significant figures, the assumed value of X, YOO and YO8, HOO and HO8, W1 and W2, R, v, u (as UU), UTE and CX.

The first computation in FINDK was the calculation of x if CX was equal to 1.0. This was followed by statements to display the input data.

The next step was to normalize the experimental results according to the input assumptions as to the values of x, u and v. The purpose of this normalization is to convert the experimental results to a form that can be compared to the results calculated by GFIND8 which assumes the absence of active hydrogen during the multiexchange reaction. If x is assumed to be infinite (i.e. k_{12} of Figure 1.6 is zero) and there is no protium in the solvent (so that k_8 must be zero), the amount of nondeuterated material produced from the methylsulfonylammonium from the salt will be zero and thus the first four values of E were normalized and placed in N so that N(1) equals zero and the sum of N(2), N(3) and N(4) equals 100%. The amount of nondeuterated product formed from the reaction of methanesulfonyl chloride (E(5)) depends on u, v and x. Thus when one of v and x and u is zero, the last four members of E were normalized as before and placed in N(5) to N(8). For cases were the values of x, u and v allow the formation of nondeuterated product the elements of E were stored in N.

After normalization of E the values of N are stored in 2 rows of the matrix C for later use. N is stored in C(1,1) to C(8,1) and in

C(1,2) to C(8,2).

The next part of FINDK uses GFIND8 to find the best values of y and H, ie. those values of y and H which, along with u, v and x best predict the values of N when substituted into the algebraic expressions. FINDK uses GFIND8 to find the best values of y and H in the following manner:

1. FINDK assigns Y00, Y08, H00 and H08 to Y0, Y8, H0 and H8 respectively.
2. FINDK calls GFIND8 using the current values of Y0, Y8, H0 and H8 as well as x and the current values of N which are stored in C(I,2). GFIND8 uses these values to generate a set of calculated multiexchange results (the vector T) most like those in C(I,2) by calculating predicted multiexchange values for each element of a 9 by 9 matrix of y, H values where Y0 is the lowest y value, Y8 the highest, H0 the lowest H value, H8 the highest and by comparing them to those in C(I,2). A detailed description of GFIND8 along with the subroutines it uses (UV and HAND) appears in subsequent sections.
3. FINDK then redefines Y0, Y8, H0, H8 by setting Y8 equal to the best y returned by GFIND8 plus three times the difference between two consecutive y values (DY in FINDK). If the new Y8 calculated is greater than Y08, the new Y8 is defined as Y08. The new Y0 is set at Y8 minus 6 DY. If the new Y0 is less than Y00, Y0 is set at Y00 and Y8 equals Y0 plus six DY. H0 and H8 are redefined in a similar manner. This process results in the new ranges of y and H to be examined in the next call of

GFIND8 to be three quarters of the previous ranges.

4. FINDK then recalls GFIND8. The process consisting of steps 2 and 3 is repeated 50 times. This was found to be sufficient to produce a vector T whose elements were the same, to the sixth significant figure, as the vector T in the previous call of GFIND8.

The next section of FINDK uses the parameters generated in GFIND8 to generate a set of results comparable to the experimental ones, ie. ones in which reaction products derived from the active hydrogen were also present. This is done using the subroutines KONST1 and MULTI2 which are described in detail at a later point in this appendix. FINDK calls KONST1 using the parameters x, y, a, H, W1, u and v. KONST1 returns a vector, K, consisting of the 12 relative rate constants shown in Figure 1.6 and A1.1. FINDK then calls MULTI2 using an initial value of the amount of the trialkyl(methylsulfonyl)ammonium salt; usually defined as 1.0 units; a value of the amount of sulfonyl chloride (0.0); the vector of rate constants, K; T1 and R. MULTI2 then calculates the relative amounts of non, mono, di and trideuterated product and passes the results back to FINDK as the first four elements of the vector M. For the reaction starting from the sulfonyl chloride KONST1 is called again using a value for W2. Then MULTI2 is recalled using a value of 0.0 for the amount of methylsulfonylammonium salt and 1.0 for the sulfonyl chloride. The results are passed back to FINDK as M(5) through M(8).

At this point FINDK calls the subroutine NORM to complete the first estimation cycle. NORM makes use of the experimental results E, the normalized experimental results N, the experimental results T

calculated by HAND (called by GFIND8) using the algebraic expressions and the simulated experimental results M. The subroutine adjusts the normalized experimental results (N) to take into account the expected effect of active hydrogen. For example if MULTI2, whose inputs are based on the estimated relative rate ratios as well as a nonzero concentration of active hydrogen, predicts that the amount of monodeuterated product from the sulfonyl chloride was 73.7% and HAND predicts an amount of 74% based on only the relative rate ratios, the value of N(6) is multiplied by 74/73.7. In this example this results in an increase in the normalized value to compensate for the fact the original normalized values (N) were based on values obtained from an experiment were active hydrogen was present. The adjusted normalized values are stored in C(I,2) to C(8,2). The remainder of NORM compares the simulated experimental results (M of this estimation cycle with the experimental values (E) and passes back the result as TS to FINDK.

The last portion of FINDK decides whether another estimation cycle should be done. The value of TS is compared to SQ. SQ is the measure of the previous estimation cycles comparison of M to E and is in fact the TS value of the previous estimation cycle. If TS was greater than SQ, or if TS was less than 8×10^{-6} lower than SQ, program execution was stopped.

A2.3 Subroutine GFIND8

This subroutine was used to find the values of y and H, that when substituted into the algebraic expressions of Appendix 1, product a set of calculated multiexchange results most like the values stored in

C(1,2) to C(8,2). To do this the subroutine GFIND8 itself calls up the subroutines UV and HAND which are described in detail in subsequent sections of this appendix.

The first task performed in GFIND8 are the definition of the size of the vectors E and T and the matrix S; Z and O as being integers; M1 and N1 as real numbers; and the calculation of the constant F1. For this subroutine the vector E has a different definition than in the main program. In GFIND8, only, E contains C(1,2) to C(8,2).

The next task performed by GFIND8 is to calculate Z1 which is the reciprocal of $x.(k_4/k_{12})$. In the cases where the ratio x was to be assumed to be very large ($k_4 >> k_{12}$), the value entered as input to FINDK was set to 0.0. This required that in GFIND8 X1 be set to zero for situations were $k_4 >> k_{12}$.

GFIND8 than finds the best y and H combination. This is done by calculating a vector, T, for each of 81 combinations of y and H. The y values used were Y0, Y0 + (Y8-Y0)/8, Y0 + 2(Y8-Y0)/8, ... and Y8; the H values used were H0, H0 + (H8-H0)/8, H0 + 2(H8-H0)/8, ... and H8 with Y0 as the lower limit to y, Y8 the upper limit to y, H0 the lower limit to H and H8 the uppper limit to H. This then, results in a nine by nine matrix of y and H values being examined by the subroutine. Each combination of y and H was passed down to the subroutine UV along with the values of E, x, v, X1 and UIE. Subroutine UV uses these to calculate the appropriate values of a, d and u. Next GFIND8 calls the subroutine HAND. HAND uses the current values of X1, y, a, d, H, u (as UU), v and x in the algebraic expressions derived in Appendix 1 to calculate the eight element vector T and returns the values to GFIND8. GFIND8 then compares T to E by calculating the sum

of squares of the element by element difference (see statement 430). This sum of squares is generated for each combination of y and H and stored in the nine by nine matrix S, the first element of which (S(,1,1)) is the sum of squares resulting from the combination of the lowest y with the lowest H, the second element, S(1,2) is the sum of squares resulting from the lowest y with the second lowest H and so on. GFIND8 then finds the smallest element of S (statements 500 to 750), recalculates the u, a, d and T values from the smallest element of S, and displays them for the last call (the fiftieth) of the subroutine.

A2.4 Subroutine KONST1

This subroutine generates a set of twelve relative rate constants for subsequent use in MULTI2. KONST1 uses the values of the rate ratios x, y, a, d, H, u, v generated earlier, either W1 for the reaction of the salt of W2 for the reaction of the sulfonyl chloride and the measured value of the isotope effect for sulfene trapping (k_8/k_9 of 1.9). The procedure followed by the subroutine was to set k_1 as 1.0. This requires that k_2 equal v and k_3 equal u. The rate constant k_4 was also set to 1.0 and this in turn requires that k_{11} equal k_4H. Since k_{10} was set to equal y and k_{10}/k_5 was assumed to be equal k_{11}/k_4, k_5 becomes y/(H·W1) for the salt and y/(H·W2) for the sulfonyl chloride with division by W1 or W2 compensating for the difference in concentrations between active hydrogen and deuterium. As a result of having set k_{10} equal to y and of setting k_9 equal to 1.0, it was convenient to satisfy the relationship:

$$y = d(a + 1)$$

or

$$y = \frac{k_{10}}{k_6}\left(\frac{k_7}{k_9} + 1\right)$$

by setting k_7 as a, k_6 as a+1 and k_8 as either 1.9 k_9/W1 or 1.9 k_9/W2. The last relative rate constant, k_{12}, was defined as k_4/x unless x was zero. If x was zero then k_{12} was set to zero. This is a consequence of the convention discussed earlier in the description of GFIND8 that an imput value of x = 0.0 means that k_4/k_{12} was assumed to be very large, i.e. infinite.

The appropriateness of defining the relative rate constants in this manner will be shown during the discussion of the control computing for MULTI2 in the following section.

2.5 Subroutine MULTI2

This subroutine uses the relative rate ratios from KONST1 to simulate the experimental results. In addition to the twelve rate constants from the previous subroutine MULTI2 requires initial concentrations of the salt and sulfonyl chloride, a value for the time step (T1) and a total simulation time (R). The inital concentrations of the salt and sulfonyl chloride were set to either one or zero as appropriate.

Subroutine MULTI2 uses the appropriate rate constant multiplied by the concentration of an intermediate or starting material and the time interval to obtain the change in concentration of each species during the time interval. This change in concentration was then used to adjust the concentration of each species. This process was repeated until the sum of the products (D(1) + D(2) + D(3) + D(4)), where D(1) is the amount of nondeuterated product, D(2) the monodeuterated, etc. was greater than 0.999999. When the simulation for the reaction from

the salt was complete the D(1) to D(4) values were multipled by 100%, placed in M(1) to M(4) and passed back to the main program. For the simulation of the reaction of methanesulfonyl chloride the results were placed in M(5) to M(8) and passed back to the main program.

In the description of KONST1 no justification for the method of calculating the relative rate constants from the predicted relative rate ratios and the assumed active deuterium to hydrogen ratio was given. This is necessary since some of the rate constants could be orders of magnitude different from others. For example k_{10}, which is related to k_5, k_6, k_7, k_8 and k_9 by the predicted relative rate ratios obtained in GFIND8 is not related to one of the set k_1, k_2 and k_3 or to one of the set k_4, k_{11} and k_{14}, may be several orders of magnitude faster than k_1 or k_4. However in KONST1 k_{10} was assigned a value of y times k_1 (or y/x times k_4) which can result in a fairly small difference between k_{10} and k_1 or k_4. In order to test whether there would be an effect on the values generated by MULTI2 as a result of having only a small difference in relative rates between members of the three sets of rate constants as exemplified by k_{10} versus k_1 or k_4 some control computing was done using a typical set of twelve rate constants. The set of rate constants investigated was:

k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	k_9	k_{10}	k_{11}	k_{12}
1.0	0.0	0.0	30.0	0.63	2.1	1.1	0.0095	1.0	63.0	15.0	1.0

The value of W1 used was 200 and the isotope effect for sulfene trapping was 1.9. The results of the simulation, with T1 = 0.001 and R = 20.0, were:

D(1)	D(2)	D(3)	D(4)
1.130438395292	3.570066155289	7.299782279387	87.99968028347

Increasing k_{10} and the other rate constants in the same set by two orders of magnitude gave:

k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	k_9	k_{10}	k_{11}	k_{12}
1.0	0.0	0.0	30.0	63.0	210.0	110.0	0.95	100.0	6300.0	15.0	1.0

and using T1 = 0.00001 and R = 20.0:

D(1)	D(2)	D(3)	D(4)
1.130438395152	3.57006605872	7.299764749949	87.99863383563

A further increase of k_{10} by two orders of magnitude gave:

k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	k_9	k_{10}	k_{11}	k_{12}
1.0	0.0	0.0	30.0	63000.0	21000.0	11000.0	95	10,000	630000	15.0	1.0

and using T1 = 0.000001 and R = 20.0

D(1)	D(2)	D(3)	D(4)
1.130438933282	3.570064982158	7.299569504771	87.98697741418

Thus the use of the first set of k was taken to be adequate for the simulation. The use of the first set allowed the use of a relatively large T1 which decreased the computation time necessary when MULTI2 was used.

The effect of varying the T1 value was also examined. With the following k:

k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	k_9	k_{10}	k_{11}	k_{12}
1.0	0.0	0.0	30.0	0.63	2.1	1.1	0.0095	1.0	63.0	15.0	1.0

T1 equal to 0.01, 0.001 and 0.0001 respectively gave the following results:

Tl	D(1)	D(2)	D(3)	D(4)
0.01	1.130438395292	3.570066155448	7.299782298339	87.99968186976
0.001	1.130438395292	3.570066155289	7.299782270387	87.99968028347
0.0001	1.130438395273	3.570066158393	7.299782833106	87.99971261131

Thus, it was assumed that any Tl chosen so that multiplication of Tl by the largest k (ie. k_{10}) would not exceed 1.0 would suffice.

The subroutine MULTI2 was also compared to the subroutine HAND (see below) in order to ensure that these subroutines would produce the same results under the appropriate conditions. When the rate constants k_5, k_8 and k_{10}, each of which include a protium concentration term were set to zero, the multiexchange simulation and the alegraic expressions were expected to give the same results. Using the following rate ratios:

u	v	x	y	a	d	H
0.05	0.1	33.3333	3.125	0.544384	2.02346	0.315625

HAND gave the results, to six significant figures, shown below for the reactions beginning with the trialkyl(methylsulfonyl)ammonium salt and methanesulfonyl chloride respectively:

$CH_3SO_2\overset{+}{N}R_3FSO_3^-$

D(1)	D(2)	D(3)	D(4)
0.990100	27.7951	25.6111	45.6037

CH_3SO_2Cl

D(1)	D(2)	D(3)	D(4)
4.43392	67.3268	10.1557	18.0836

The subroutine MULTI2 gave the following results:

$CH_3SO_2\overset{+}{N}R_3FSO_3^-$

D(1)	D(2)	D(3)	D(4)
0.990099	27.7951	25.6111	45.6036

CH_3SO_2Cl

D(1)	D(2)	D(3)	D(4)
4.43392	67.3268	10.1557	18.0835

The results were taken to indicate that MULTI2 was equivalent to the algebraic expressions in the limiting case.

A2.6 Subroutine NORM

This subroutine generates the values of the normalized experimental results to be used by GFIND8 in the next estimation cycle. After normalization of the experimental results to produce the vector, N, the first estimation of y and H was made as if these values used arose from condition where the multiexchange reaction was carried out in rigorously pure deuterium oxide. By comparison of the value predicted by the algebraic expressions (HAND) with the result from the simulation (MULTI2) the normalized experimental values were corrected to what they would have been if there was no protium present during the multiexchange. For example, if the value for the monodeuterated product for the multiexchange of methanesulfonyl chloride was predicted to be 74.2079 by HAND and the same value predicted by MULTI2 was 73.7603 the

normalized experimental value was multipled by 74.2079/73.7603. Thus, in the next estimation cycle GFIND8 was able to employ values that more closely resemble those demanded by the assumption used in the derivation of the six algebraic expressions and an improved set of parameters would result. These corrected values which are stored locally in NORM as the vector C are returned to the main program and stored in C(1,2) to C(8,2).

The remainder of NORM compares the results of the simulation with the experimental results by calculating the sum of squares of the element by element difference between M and E (see statement 440). The result was passed back to FINDK as TS.

A2.7 Subroutine UV

This subroutine calculates the rate ratios u (k_3/k_1), a (k_7/k_9) and d (k_{10}/k_6) from the experimental multiexchange results (E) and the other rate ratios. If the value of u (UU in the program) was to be held constant the constant UTE was given a value of 100.0 in the input to the main program.

The expressions for a and u (A and UU in the subroutine) were derived from the algebraic expressions of appendix 1 as follows. The expression for E(6), D_1^T in the expressions derived for the reactions starting from methanesulfonyl chloride, was

$$E(6) = \left(\frac{1}{2x} + \frac{1}{ad} + \frac{1}{2adx} + \frac{1}{2adI} + \frac{1}{a} + \frac{1}{2x}\right)(E(7) + E(8))$$

$$- \frac{1}{a}\left[\frac{3xv}{3x+1}\left((a+1)(E(6) - \frac{1}{2x}(E(7) + E(8))\right.\right.$$

$$\left.\left. - \left(\frac{1}{d} + \frac{1}{2dx} + \frac{1}{2dI}\right)(E(7) + E(8))\right)\right]$$

Substitution of H for 1/I, DS for E(7) + E(8) and PP for $\frac{3xv}{3x+1}$ followed by expansion and collection of the DS terms gave:

$$E(6) = (\frac{1}{2x} + \frac{1}{ad} + \frac{1}{2adx} + \frac{H}{2ad} + \frac{1}{a} + \frac{1}{2x} + \frac{PP(a+1)}{2xa} + \frac{PP}{ad}$$

$$+ \frac{PP}{2adx} + \frac{PPH}{2ad})DS - PP\frac{(a+1)}{a} E(6)$$

$$E(6) = (\frac{1}{2x} + \frac{PP+1}{ad} + \frac{PP+1}{2adx} + \frac{(PP+1)H}{2ad} + \frac{1}{a} + \frac{1}{2ax} + \frac{PP(a+1)}{2ax}) DS$$

$$- PP\frac{(a+1)}{a} E(6)$$

Substitution of $y/(a+1)$ for d and collection of the a and $(a+1)/a$ terms gave:

$$E(6) = (\frac{1}{2x} + \frac{(PP+1)(a+1)}{ay} + \frac{(PP+1)(a+1)}{2axy} + \frac{(PP+1)(a+1)H}{2dy}$$

$$+ \frac{1}{a} + \frac{1}{2ax} + \frac{PP(a+1)}{2ax}) DS - PP\frac{(a+1)}{a} E(6)$$

$$E(6) = \frac{a+1}{a}\{(\frac{PP+1}{y} + \frac{PP+1}{2xy} + \frac{(PP+1)H}{2y} + \frac{PP}{2x}) DS - PPE(6)\}$$

$$= \frac{1}{a}(1 + \frac{1}{2x}) DS + \frac{1}{2x} DS$$

$$E(6) - \frac{DS}{2x} = \frac{a+1}{a}\{(\frac{PP+1}{y} + \frac{PP+1}{2xy} + \frac{(PP+1)H}{2y} + \frac{PP}{2x}) DS$$

$$- PP\ E(6)\} + \frac{1}{a}(1 + \frac{1}{2x})DS$$

Using X1 for the 1/x the above expression was simplified using the following three terms:

$$AA = E(6) - .5DSX1$$

$$BB = (PP+1)(1/y + .5X1/y + .5H/y)DS - PP\ E(6)$$

$$CC = (1 + .5X1)DS$$

to give

$$AA = \frac{a+1}{a} BB + \frac{1}{a} CC$$

The expression for a was

$$A = (BB + CC)/(AA - BB)$$

The equation for E(5), D_0^T for the reaction from methanesulfonyl chloride, was rearranged to give an expression for u (K_3/k_1) as follows:

$$E(5) = (u + \frac{v}{3x+1})[(a+1)(E(6) - \frac{E(7)+E(8)}{2x}]$$

$$- (\frac{1}{d} + \frac{1}{2dx} + \frac{1}{2dI})(E(7) + E(8))]$$

$$E(5) - \frac{v}{3x+1}[(a+1)(E(6) - 0.5\ DSX1) - (\frac{1}{d} + \frac{0.5\ X1}{d} + \frac{0.5H}{d})DS]$$

$$= u[(a+1)(E(6) - .5DSX2) - (\frac{1}{d} + \frac{0.5X1}{d} + \frac{0.5H}{d})DS]$$

After definition of the term in square brackets as SS the expression

for u was

$$u = \frac{E(5)}{SS} - \frac{v}{3x+1}$$

As was mentioned in the discussion of GFIND8 an infinite value of x (k_4/k_{12}) was entered into the program by using the convention that when the input value of x was zero, the value of x was taken to be very large, i.e. infinite. Thus the last "if statement" of the subroutine sets u as E(5)/SS if x was assumed to be very large.

A2.8 Subroutine HAND

This subroutine calculates the multiexchange results using the rate ratios generated in GFIND8. The values calculated are those that would arise from these rate ratios if protium was not present in the reaction system, ie. those obtained by substitution into the algebraic expressions derived in Appendix 1.

The first part of the subroutine initializes the values of the constants used. If the rate ratio x was assumed to be very large, the value of its reciprocal X1, was set to zero in GFIND8 before HAND was called. As a result the terms that include X1 were allowed to remain at zero in this case. The remainder of the subroutine calculates the compositions for the reaction of the salt and for the sulfonyl chloride. The values were stored in T in the usual manner and passed back to GFIND8 which in turn passes the values back to the main program.

```
      PROGRAM FINDK(INPUT,OUTPUT)
C
C        THIS PROGRAM GENERATES A SERIES OF TWELVE RELATIVE RATE
C     CONSTANTS WHICH BEST DESCRIBE THE EXPERIMENTAL RESULTS USING
C     THE ASSUMED VALUES OF K4/K12 (X),THE RATIO OF K2/K1 (V) AND THE
C     RATIO OF ACTIVE DEUTERIUM TO HYDROGEN (W1).
C        THE PROGRAMMING WAS CARRIED OUT TO A MINIMUM OF SIX SIGNIFI-
C     GANT FIGURES.
C
C        THIS SECTION READS THE EXPERIMENTAL RESULTS AS A VECTOR E WHERE
C     THE RESULTS FROM THE MULTIEXCHANGE REACTION WITH A TRIALKYL(METH-
C     YL)SULFONYL AMMONIUM SALT AS THE STARTING MATERIAL WERE THE FIRST
C     FOUR ELEMENTS AND THE VALUES FROM THE REACTION WITH METHANESULFON-
C     YL CHLORIDE AS THE STARTING MATERIAL WERE THE LAST FOUR ELEMENTS.
C        IF X WAS INPUTTED AS ZERO THIS WAS TAKEN TO MEAN THAT THE
C     VALUE OF X WAS ACTUALLY INFINITE.THIS MEANT THAT THE RELATIVE
C     RATE CONSTANT K12 WAS SET TO BE ZERO.
C        Y00 WAS THE LOWER LIMIT AND Y08 THE UPPER LIMIT FOR Y.
C        H00 WAS THE LOWER LIMIT AND H08 THE UPPER LIMIT FOR H.
C        T1 WAS THE "TIME INTERVAL" USED IN SUBROUTINE MULTI2 AND R WAS
C      THE TOTAL "SIMULATION TIME" FOR MULTI2.
C        V WAS THE ASSUMED VALUE FOR K2/K1 AND UU (OR U) WAS THE VALUE
C     FOR K3/K1.
C        UTE WAS A TEST CONSTANT USED IN SUBROUTINE UV. IF UTE WAS INPUT
C     AS EQUAL TO 100.0 THE VALUE OF UU REMAINED EQUAL TO ITS INPUT
C     VALUE.
C
      REAL E(8),N(8),M(8),T(8),Q(4),C(8,2),K(12)
      READ*,E,X,Y00,Y08,H00,H08,W1,R,V,UU,UTE
      READ*,W2
      READ*,CX
      IF(CX.EQ.1.0) GO TO 3
      DX=E(1)-1.9*E(2)/W1
      X=(100.0-DX)/(3.0*DX)
    3 CONTINUE
      PRINT*,"   ",
      PRINT*,"E IS",E
      PRINT*,"   ",
      PRINT*,"DEUT/PROT RATIO FOR SALT WAS",W1
      PRINT*,"   ",
      PRINT*,"DEUT/PROT RATIO FOR SULFONYL CHLORIDE WAS",W2
      PRINT*,"   ",
      PRINT*,"UU,V,AND UTE ARE ";UU,V,UTE
      PRINT*,"X,Y00,Y08,H00 AND H08 ARE ",X,Y00,Y08,H00,H08
C
C        THE NEXT SECTION NORMALIZES THE EXPERIMENTAL RESULTS AND PUTS
C     THEM IN THE VECTOR N.IT ALSO PRINTS THEM FOR INSPECTION.
C
      IF(X.EQ.0.0) GO TO 13
      DO 4 I=1,4
```

```
    4 N(I)=E(I)
      IF (UU.EQ.0.0.AND.V.EQ.0.0) GO TO 11
      DO 5 I=5,8
    5 N(I)=E(I)
      GO TO 17
   13 N(1)=0.0
      DO 8 I=2,4
    8 N(I)=E(I)/(1-.01*E(1))
      IF (UU.EQ.0.0) GO TO 11
      DO 9 I=5,8
    9 N(I)=E(I)
      GO TO 17
   11 N(5)=0.0
      DO 12 I=6,8
   12 N(I)=E(I)/(1-.01*E(5))
   17 SQ=1.0E10
      PRINT*," "
      PRINT*,"N IS",N
C
C       DO LOOP 10 PLACES THE VECTOR N IN BOTH COLUMNS OF THE MATRIX C.
C
      DO 10 I=1,8
      C(I,1)=N(I)
   10 C(I,2)=N(I)
C
C       DO LOOP 80 LIMITS THE MAXIMUM NUMBER OF TIMES THAT A SEARCH FOR
C     K WAS MADE.
C
      DO 80 ICYCLE=1,20
C
C       THE FOLLOWING FOUR STATEMENTS INITIALIAZE Y0,Y8,H0 AND H8.
C     Y0 AND Y8 WERE THE LOWER AND UPPER LIMITS OF Y USED IN SUBROUTINE
C     GFIND8. H0 AND H8 WERE THE ANALOGOUS VALUES FOR H.
C
      Y0=Y00
      Y8=Y08
      H0=H00
      H8=H08
C
C       DO LOOP 50 CAUSED THE SUBROUTINE GFIND8 TO BE EXECUTED 50 TIMES
C     AS WELL AS REDEFINING THE LIMITS OF Y AND H TO BE USED THE NEXT
C     TIME GFIND8 WAS CALLED.
C
      DO 50 I=1,100
C
C       DY AND DH CALCULATED BELOW CORRESPOND TO M1 AND N1 OF GFIND8.
C     THE PRINT STATEMENT ALLOWS INSPECTION OF THE LIMITS FOR Y AND H
C     EACH TIME GFIND8 WAS CALLED.
C
      DY=(Y8-Y0)/8
```

```
      DH=(H8-H0)/8
      CALL GFIND8(X,Y0,Y8,H0,H8,C(1,2),Y,H,A,D,T,I,V,UU,UTE)
C
C        THE NEXT SIX STATEMENTS RESET THE LIMITS OF H (H0 AND H8) SO
C     THAT THE RANGE WAS THREE QUARTERS OF THE PREVIOUS RANGE OF H.
C
      H8=H+3*DH
      IF (H8.GT.H08) H8=H08
      H0=H8-6*DH
      IF(H0.GE.H00) GO TO 40
      H0=H00
      H8=H0+6*DH
C
C        THE NEXT SIX STATEMENTS RESET THE LIMITS OF Y AS WAS DONE ABOVE
C     FOR H.
C
   40 Y8=Y+3*DY
      IF(Y8.GT.Y08) Y8=Y08
      Y0=Y8-6*DY
      IF(Y0.GE.Y00) GO TO 50
      Y0=Y00
      Y8=Y0+6*DY
   50 CONTINUE
      T1=.8/Y
C
C        KONST1 CONVERTS THE RATE RATIOS X,Y,A,D,H,UU, AND V TO THE
C     TWELVE RELATIVE RATE CONSTANTS K.IT ALSO MAKES USE OF W1 AND THE
C     MEASURED VALUE OF 1.9 FOR THE KINETIC ISOTOPE EFFECT FOR SULFENE
C     TRAPPING.
C        SINCE D=Y/(A+1) THE VALUE OF D WAS NOT PASSED DOWN TO THE
C     SUBROUTINE.
C
      CALL KONST1(X,Y,A,H,W1,K,UU,V)
C
C        THE NEXT TWO STATEMENTS CARRY OUT THE SIMULATION FOR THE
C     MULTIEXCHANGE REACTIONS STARTING FROM THE TRIALKYL(METHYLSULFON-
C     YL)AMMONIUM SALTS AND PLACES THEM IN THE FIRST FOUR ELEMENTS OF M.
C
      Q(1)=1.0
      CALL MULTI2(Q,0.0,K,T1,R,M)
C
C        THE NEXT TWO STATEMENTS CARRY OUT THE ABOVE CALCULATION WITH
C     METHANESULFONYL CHLORIDE AS THE STARTING MATERIAL AND PLACES THE
C     VALUES IN THE LAST FOUR ELEMENTS OF M.
C
      CALL KONST1(X,Y,A,H,W2,K,UU,V)
      Q(1)=0.0
      CALL MULTI2(Q,1.0,K,T1,R,M(5))
C
C        SUBROUTINE NORM ADJUSTS THE VALUES OF M AND PLACES THE RESULTS
```

```
C     IN C(I,2) FOR USE IN THE NEXT ESTIMATION CYCLE.IT ALSO COMPARES
C     M WITH E BY CALCULATION OF THE SUM OF SQUARES OF THE ELEMENT BY
C     ELEMENT DIFFERENCES AND PASSES UP THE RESULT TO THE MAIN PROGRAM
C     AS TS.
C
      CALL NORM(E,N,T,M,C(1,2),TS)
C
C        THE FOLLOWING IF STATEMENT TESTS WHETHER THE CURRENT VALUE OF
C     TS IS GREATER THAN THE VALUE OF THE PREVIOUS CYCLE (STORED AS SQ).
C     THE INITIAL VALUE OF SQ WAS SET AT 1.0E10 TO ENSURE THAT THE
C     ESTIMATION CYCLE WOULD BE RUN AT LEAST TWICE.
C
      IF(TS.GT.SQ) GO TO 90
C
C        THE FOLLOWING STATEMENT ASSIGNS THE CURRENT VALUE OF TS TO SQ
C     FOR USE AS A TEST VALUE IN THE NEXT CYCLE.
C
      SQ=TS
C
C        THE NEXT FOUR STATEMENTS CALCULATE THE DIFFERENCE BETWEEN
C     C(I,1) AND C(I,2). C(I,1)STORES THE VALUES USED AS INPUT FOR
C     GFIND8 IN THE CURRENT ESTIMATION CYCLE. C(I,2) STORES THE VALUES
C     RETURNED BY SUBROUTINE NORM FOR USE IN THE NEXT CYCLE. IF C(I,1)
C     AND C(I,2) WOULD BE IDENTICAL OR VERY SIMILAR THEN THE NEXT
C     ESTIMATION CYCLE WOULD PRODUCE IDENTICAL OR VERY SIMILAR RESULTS.
C     THUS FURTHER COMPUTATION WOULD NOT RESULT IN AN IMPROVED SET OF K.
C     AND THE EXECUTION OF THE PROG9AM WAS TERMINATED.
C
      SUM=0.0
      DO 60 I=1,8
   60 SUM=SUM+ABS(C(I,2)-C(I,1))
      IF(SUM.LT.8.0E-6) GO TO 90
C
C        DO LOOP 70 ASSIGNS THE VALUES OF C(I,2) INTO C(I,1) FOR USE IN
C     THE NEXT CYCLE.
C
      DO 70 I=1,8
   70 C(I,1)=C(I,2)
   80 CONTINUE
   90 STOP
      END
```

```
      SUBROUTINE GFIND8(X,Y0,Y8,H0,H8,E,Y,H,A,D,T,II,V,UU,UTE)
C
C        THIS SUBROUTINE SEARCHES FOR THE BEST VALUES OF Y AND H FOR
C     GIVEN VALUES OF X AND V. IT DOES SO BY VARYING Y AND H BETWEEN
C     THE GIVEN LIMITS AND CALCULATING THE MULTIEXCHANGE RESULTS AS PRE-
C     DICTED BY THE DERIVED ALGEBRAIC EXPRESSIONS, STORING THEM IN THE
C     VECTOR T.T WAS THEN COMPARED TO THE VALUES STORED IN C(I,2) WHICH
C     WERE PASSED DODOWN AND STORED LOCALLY AS E.
C       THE COMPARISON WAS MADE USING THE SUM OF SQUARES OF THE ELEMENT
C     BY ELEMENT DIFFERENCE BETWEEN THE TWO VECTORS.( SEE DO LOOP 430).
C
      DIMENSION E(8),T(8),S(9,9)
      INTEGER Z,O
      REAL M1,N1
      F1=E(6)/(E(7)+E(8))
C
C        THE NEXT TWO STATEMENTS ENSURE THAT X1 HAS THE APPROPRIATE
C     VALUE. THUS AS DESCRIBED IN THE MAIN PROGRAM IF X WAS INPUT AS
C     ZERO THEN X1 SHOULD BE EQUAL TO ZERO.
C
      X1=0.0
      IF (X.NE.0.0) X1=1/X
C
C        THE NEXT TWO STATEMENTS CALCULATE THE AMOUNTS Y AND H WERE
C     INCREMENTED. SINCE THIS INCREMENT WAS ONE EIGHTH OF THE DIFFERENCE
C     BETWEEN THE UPPER AND LOWER LIMITS THIS SUBROUTINE EXAMINED
C     81 COMBINATIONS OF Y AND H.
C
      M1=(Y8-Y0)/8
      N1=(H8-H0)/8
C
C        THE INITIAL VALUE OF Y=Y0 WAS PAIRED WITH NINE VALUES OF H
C     VARYING FROM H0 TO H8 WHICH WERE PASSED DOWN FROM THE MAIN
C     PROGRAM. FOR EACH Y,H PAIR THE SUBROUTINE UV WAS CALLED TO CA-
C     CULATE THE APPROPRIATE VALIES OF A,D AND U. THE SUBROUTINE HAND
C     WAS THEN CALLED TO GENERATE T. THE DO LOOP 430 PREFORMS THE
C     COMPARISON BETWEEN T AND E. AFTER ALL NINE VALUES OF H WERE USED
C     THE PROCESS WAS REPEATED WITH THE NEXT HIGHER Y UNTIL ALL NINE
C     Y VALUES WERE USED.THIS RESULTED IN A NINE BY NINE MATRIX OF SUMS
C     SQUARES.
C
      Y=Y0
      DO 470 I=1,9
      H=H0
      DO 450 Z=1,9
      CALL UV(E,X,V,UU,X1,A,D,Y,H,UTE)
      CALL HAND(X1,Y,A,D,H,T,UU,V,X)
      S(I,Z) = 0
      DO 430 O=1,8
  430 S(I,Z)=S(I,Z)+(E(O)-T(O))**2
```

```
  450 H=H+N1
  470 Y=Y+M1
C
C       THE DO LOOP 570 SEARCHES THE NINE BY NINE MATRIX S FOR THE
C     SMALLEST ELEMENT AND STORES ITS POSITION USING IA AND IB.
C
  500 W=S(1,1)
      DO 570 I=1,9
      DO 570 Z=1,9
      IF(W.LT.S(I,Z)) GO TO 570
      W= S(I,Z)
      IA=I
      IB=Z
  570 CONTINUE
C
C       THE NEXT FOUR STATEMENTS RETREIVE THE Y AND H VALUES THAT GAVE
C     THE SMALLEST ELEMENT OF S, RECALCULATES A,D AND UU AS WELL AS T.
C
      Y=Y0+(IA-1)*M1
      H=H0+(IB-1)*N1
      CALL UV(E,X,V,UU,X1,A,D,Y,H,UTE)
      CALL HAND(X1,Y,A,D,H,T,UU,V,X)
C
C       THE LAST STATEMENTS PRINT THE RESULTS FOR THE FINAL TIME GFIND8
C     WAS CALLED BY THE MAIN PROGRAM IN THE CURRENT ESTIMATION CYCLE.
C
      IF(II.NE.50) RETURN
      PRINT*,"  ",
      PRINT*,"X,Y0,Y8,H0,H8 ARE  ",X,Y0,Y8,H0,H8
      PRINT*,"UU DETERMINED IS ",UU
      PRINT*,"H INCREASES ACROSS THE PAGE BY INCREMENTS OF",N1
      PRINT*,"Y INCREASES DOWN THE PAGE BY INCREMENTS OF", M1
      PRINT*,"  ",
      PRINT*,"THE SMALLEST ELEMENT,S(",IA,",",IB,") IS",W
      PRINT*,"THE FIVE PARAMETERS ARE", X,Y,A,D,H
      PRINT*,"TEASE ARE ",T
      PRINT*,"  ",
   55 CONTINUE
      RETURN
      END
```

```
      SUBROUTINE KONST1(X,Y,A,H,W1,K,UU,V)
C
C        THIS SUBROUTINE USES THE RELATIVE RATE RATIOS X,Y,A,H,H2,U AND
C     V ALONG WITH W1 AND THE VALUE OF THE KINETIC ISOTOPE EFFECT
C     FOR SULFENE TRAPPING (1.9) TO GENERATE THE TWELVE RATE CONSTANTS
C     NECESSARY TO SIMULATE THE MULTIEXCHANGE REACTION.
C        THESE K WERE USED IN SUBROUTINE MULTI2.
C
      REAL K(12)
      K(1)=1
      K(2)=V*K(1)
      K(3)=UU*K(1)
      K(4)=1.0
      H2=H
      K(5)=Y/(H2*W1)
      K(6)=A+1
      K(7)=A
      K(8)=1.9/W1
      K(9)=1.0
      K(10)=Y
      K(11)=H*K(4)
      K(12)=0.0
      IF (X.NE.0[illegible] K(12)=K(4)/X
C
C        THIS IF STATEMENT ALLOWS FOR THE CASE WERE X WAS NOT ASSUMED TO
C     BE EQUAL TO INFINITY.
C
      PRINT*,"  ",
      PRINT*, K
      PRINT*,"  ",
      PRINT*,"DEUT/PROT RATIO USED WAS ",W1
      PRINT*,"    ",
      RETURN
      END
```

```
      SUBROUTINE MULTI2(Q,CC,K,T1,R,D)
C
C       THIS SUBROUTINE WAS USED TO SIMULATE THE MULTIEXCHANGE
C     REACTION WITH EITHER A QUATERNARY(METHYLSULFONYL)AMMONIUM SALT
C     -Q(1)- OR METHANESULFONYL CHLORIDE -C(1)- AS THE STARTING
C     MATERIAL.
C        THE NECESSARY INPUT CONSISTS OF A VECTOR OF TWELVE RELATIVE
C     RATE CONSTANTS WHICH WERE OBTAINED FROM KONST1, A STEP SIZE T,
C     MAXIMUM SIMULATION TIME R AND THE INITIAL VALUES OF Q(1) AND C(1).
C
      DIMENSION K(12),S(3),Z(3),Q(4),D(4),C(1)
      INTEGER G
      REAL K
      C(1)=CC
      G=R/T1+1
      PRINT*,"  ",
      PRINT*,"THE INITIAL CONCENTRATIONS ARE ",Q(1),C(1)
      PRINT*,"      ",
      WRITE*,"THE RATE CONSTANTS K(1TO12) ARE",K
      PRINT*,"      ",
      PRINT*,"STEP SIZE(T1) FOR DT IS ",T1
      WRITE*,"TOTAL SIMULATION TIME IS",R
      PRINT*,"      ",
      PRINT*,"G = ",G
      PRINT*,"  ",
      T = 0
C
C       THE NEXT THREE STATEMENTS INITIALIZE THE CONCENTRATIONS OF THE
C     INTERMEDIATES AND PRODUCTS.
C
      DO 10 I=1,3
   10 S(I)=Z(I)=D(I)=0.0
      Q(2)=Q(3)=Q(4)=D(4)=0.0
      DO 560 KK=1,G
      T=T+T1
C
C       THE FOLLOWING SECTION CALCULATES THE CHANGE IN CONCENTRATION OF
C     EACH SPECIES DURING THE TIME INTERVAL BY MULTIPICATON OF THE RATE
C     CONSTANTS BY THE CONCENTRATIONS AT THIS POINT OF THE REACTION.
C     MULTIPLICATION OF EACH TERM BY THE TIME INTERVAL WAS LEFT UNTIL
C     THE NEXT SECTION FOR CONVENIENCE.
C
C       THE IF STATEMENTS SET THE CONCENTRATION OF EACH SPECIES TO ZERO
C     IF THE VALUE FALLS BELOW 1E-25.
C
      IF (C(1) .LE. 1.E-25) C(1) = 0
      C1=-K(1)*C(1)-K(2)*C(1)-K(3)*C(1)
      IF (Q(1) .LE. 1.E-25) Q(1) = 0.
      IF (Z(1) .LE. 1.E-25) Z(1) = 0.
      Q1=K(2)*C(1)-3*K(4)*Q(1)-K(12)*Q(1)+K(5)*Z(1)
```

```
      IF (S(1) .LE. 1.E-25) S(1) = 0.
      D1=K(3)*C(1)+K(8)*S(1)+K(12)*Q(1)
      IF (Q(2) .LE. 1.E-25) Q(2) = 0.
      Z1=3*K(4)*Q(1)-K(5)*Z(1)+K(7)*S(1)-K(6)*Z(1)+K(11)*Q(2)-K(10)*Z(1)
      S1=K(1)*C(1)+K(6)*Z(1)-K(7)*S(1)-K(8)*S(1)-K(9)*S(1)
      IF (Z(2) .LE. 1.E-25) Z(2) = 0.
      Q2=K(10)*Z(1)-K(11)*Q(2)-K(12)*Q(2)-2*K(4)*Q(2)+K(5)*Z(2)
      IF (S(2) .LE. 1.E-25) S(2) = 0.
      D2=K(9)*S(1)+K(12)*Q(2)+K(8)*S(2)
      IF (Q(3) .LE. 1.E-25) Q(3) = 0.
      Z2=2*K(4)*Q(2)-K(5)*Z(2)-K(6)*Z(2)+K(7)*S(2)-K(10)*Z(2)+2*K(11)*
     1Q(3)
      S2=K(6)*Z(2)-K(7)*S(2)-K(8)*S(2)-K(9)*S(2)
      IF (Z(3) .LE. 1.E-25) Z(3) = 0.
      Q3=K(10)*Z(2)-2*K(11)*Q(3)-K(12)*Q(3)-K(4)*Q(3)+K(5)*Z(3)
      IF (S(3) .LE. 1.E-25) S(3) = 0.
      D3=K(9)*S(2)+K(12)*Q(3)+K(8)*S(3)
      Z3=K(4)*Q(3)-K(5)*Z(3)-K(6)*Z(3)+K(7)*S(3)-K(10)*Z(3)+3*K(11)*Q(4)
      IF (Q(4) .LE. 1.E-25) Q(4) = 0.
      S3=K(6)*Z(3)-K(7)*S(3)-K(8)*S(3)-K(9)*S(3)
      Q4=K(10)*Z(3)-3*K(11)*Q(4)-K(12)*Q(4)
      D4=K(9)*S(3)+K(12)*Q(4)
C
C        THE NEXT SECTION COMPLETES THE CALCULATION OF THE CHANGE IN
C     CONCENTRATIONS AND ADJUSTS THE CONCENTRATION OF EACH SPECIES.
C
      C(1)=C(1)+C1*T1
      Q(1)=Q(1)+Q1*T1
      D(1)=D(1)+D1*T1
      Z(1)=Z(1)+Z1*T1
      S(1)=S(1)+S1*T1
      Q(2)=Q(2)+Q2*T1
      D(2)=D(2)+D2*T1
      Z(2)=Z(2)+Z2*T1
      S(2)=S(2)+S2*T1
      Q(3)=Q(3)+Q3*T1
      D(3)=D(3)+D3*T1
      Z(3)=Z(3)+Z3*T1
      S(3)=S(3)+S3*T1
      Q(4)=Q(4)+Q4*T1
      D(4)=D(4)+D4*T1
C
C        THE NEXT TWO STATEMENTS TEST IF PRODUCT FORMATION HAD REACHED
C     THE 99.9999 PERCENT LEVEL.IF SO THE SIMULATION WAS TERMINATED.
C
      DTOT=D(1)+D(2)+D(3)+D(4)
      IF(DTOT.GT..999999) GO TO 570
C
C        THE LAST PART OF THE SUBROUTINE PRINTS THE CONCENTRATIONS AT
C     THE TIME THE SIMULATION WAS TERMINATED. THE VALUES OF D WERE
```

```
C     INCREASED BY 100 TIMES SO THAT THEY APPEAR AS PERCENTAGES.
C
  560 CONTINUE
  570 PRINT*,"S(1,2,3) ARE ",S
      PRINT*,"Z(1,2,3) ARE ",Z
      PRINT*,"Q(1,2,3,4) ARE ",Q
      PRINT*,"          ",
      PRINT*,"C(1) IS ",C(1)
      D(1)=D(1)*100.0
      D(2)=D(2)*100.0
      D(3)=D(3)*100.0
      D(4)=D(4)*100.0
      PRINT*,"  ",
      PRINT*,"DTOTAL IS",DTOT
      PRINT*,"          ",
      PRINT*,"D(1,2,3,4) ARE ",D
      PRINT*,"  ",
      PRINT*,"KK = ",KK
      STOP
      END
```

```
      SUBROUTINE NORM(E,N,H,M,C,TS)
C
C        THE SUBROUTINE USES THE EXPERIMENTAL VALUES WHICH WERE PASSED
C     DOWN AS E, THE VALUES IN C(I,2) WHICH WERE PASSED DOWN TO GFIND8
C     AND STORED AS C,THE VALUES OF T WHICH WERE CALCULATED BY HAND AND-
C     STORED LOCALLY AS H,THE SIMULATED VALUES M AND THE NORMALIZED EX-
C     PERIMENTAL VALUES N.
C
      REAL H(8),M(8),C(8),N(8),E(8),S(8)
      DO 60 I=1,8
   60 C(I)=0.0
C
C        THE FIRST SECTION CALCULATES C(1) TO C(8), NORMALIZES C(1)
C     TO C(4) TO 100 PERCENT AND C(5) TO C(8) TO 100 RERCENT.
C
      C(1)=N(1)*H(1)/M(1)
      C(2)=N(2)*H(2)/M(2)
      C(3)=N(3)*H(3)/M(3)
      C(4)=N(4)*H(4)/M(4)
      C(5)=N(5)*H(5)/M(5)
      C(6)=N(6)*H(6)/M(6)
      C(7)=N(7)*H(7)/M(7)
      C(8)=N(8)*H(8)/M(8)
      S1=C(1)+C(2)+C(3)+C(4)
      S2=C(5)+C(6)+C(7)+C(8)
      C(1)=C(1)/S1
      C(2)=C(2)/S1
      C(3)=C(3)/S1
      C(4)=C(4)/S1
      C(5)=C(5)/S2
      C(6)=C(6)/S2
      C(7)=C(7)/S2
      C(8)=C(8)/S2
      DO 33 I=1,8
   33 C(I)=100.0*C(I)
C
C        THE NEXT SECTION PRINTS THE VALUES OF C.
C
      PRINT*," "
      PRINT*,"SALT VALUES ARE",          C(1),C(2),C(3),C(4)
      PRINT*," "
      PRINT*,"SULFONYL CHLORIDE VALUES ARE",C(5),C(6),C(7),C(8)
C
C        THE LAST SECTION COMPARES THE SIMULATED EXPERIMENTAL VALUES
C     OBTAINED IN THIS ESTIMATION CYCLE WITH THE ACTUAL EXPERIMENTAL
C     VALUES BY CALCULATION OF THE SUM OF SQUARES OF THE ELEMENT BY
C     ELEMENT DIFFERENCE BETWEEN M AND E.
C
      DO 440 I=1,8
  440 S(I)=(M(I)-E(I))**2
```

```
TS=S(1)+S(2)+S(3)+S(4)+S(5)+S(6)+S(7)+S(8)
PRINT*,"    ",
PRINT*,"SUM OF SQUARES FOR 8 VALUES IS", TS
PRINT*,"    ",
RETURN
END
```

```
      SUBROUTINE UV(E,X,V,UU,X1,A,D,Y,H,UTE)
C
C       THIS SUBROUTINE CALCULATES THE RATE RATIOS A,D AND U GIVEN
C     VALUES OF X,Y,V,H AND E.
C       THE VECTOR E WAS PASSED DOWN FROM THE SUBROUTINE GFIND8. IF
C     THE VALUE OF U (UU) WAS TO BE HELD CONSTANT OR EQUAL TO ZERO THIS
C     WAS ACCOMPLISHED BY SETTING UU EQUAL TO ZERO OR UTE EQUAL TO
C     100.0.
C
      DIMENSION E(8)
      DS=E(7)+E(8)
      PP=3*X*V/(3*X+1)
      AA=E(6)-.5*DS*X1
      CC=(1.0+.5*X1)*DS
      BB=(PP+1)*(1/Y+.5*X1/Y+.5*H/Y)*DS+.5*PP*X1-PP*E(6)
      A=(BB+CC)/(AA-BB)
      D=Y/(A+1)
      SS=(A+1)*(E(6)-.5*DS*X1)-(1/D+.5*X1/D+.5*H/D)*DS
      IF(UU.EQ.0.0.OR.UTE.EQ.100.0) RETURN
      UU=E(5)/SS-V/(3*X+1)
      IF(X.EQ.0.0) UU=E(5)/SS
      RETURN
      END
```

```
      SUBROUTINE HAND(X1,Y,A,D,H,T,UU,V,X)
C
C        THIS SUBROUTINE WAS USED TO CALCULATE THE VACTOR T USING THE
C     DERIVED ALGEBRAIC EXPRESSIONS WHICH WERE BASED ON THE ASSUPTION
C     THAT PROTIUM WAS NOT PRESENT DURING THE MULTIEXCHANGE REACTION.
C
      DIMENSION T(8)
      REAL J,K,L,M,N
      A1=0
      C=0
      G=0
      J=0
      P=0
      M=0.0
      PP=3*X*V/(3*X+1)
C
C        THE NEXT STATEMENT ALLOWS THE FOLLOWING SIX CONSTANTS TO
C     REMAIN EQUAL TO ZERO WHEN X1 WAS ZERO.
C
      IF (X1.EQ.0.0) GO TO 220
      A1=X1
      C=A1/Y
      G=A1/2
      J=C/2
      M=G/A
      P=A1/(2*A*D)
  220 B=1/Y
      F=2*H*B
      K=F/4
      L=1/A
      N=L/D
      Q=N*H/2
C
C        THE NEXT NINE STATEMENTS CALCULATE THE PERCENTAGE COMPOSITIONS
C     FOR THE REACTION FROM THE QUATERNARY(METHYLSULFONYL)AMMONIUM SALT
C     SO THAT THE TOTAL EQUALS 100 PERCENT AND PLACES THEM IN T(1) TO
C     T(4).
C
      T(4)=1
      T(3)=(A1+B+C+F)*T(4)
```

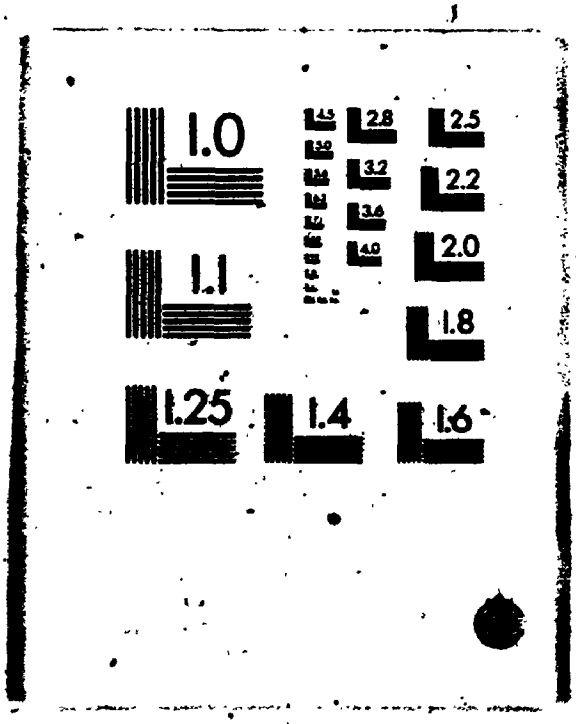
```
      T(2)=(G+B+J+K)*(T(3)+T(4))
      T(1)=(A1/3)*(T(2)+T(3)+T(4))
      S1=T(1)+T(2)+T(3)+T(4)
      T(1)=100*T(1)/S1
      T(2)=100*T(2)/S1
      T(3)=100*T(3)/S1
      T(4)=100*T(4)/S1
C
C        THE NEXT ELEVEN STATEMENTS CALCULATE THE ANALOGOUS VALUES FOR
C     THE REACTION WITH METHANESULFONYL CHLORIDE AS THE STARTING
C     MATERIAL AND PLACES THE RESULTS IN T(5) TO T(8).
C
      T(8)=1
      T(7)=(A1+B+C+F)*T(8)
      TT1=(G+N+P+Q+L+M)
      TT2=(.5*(A+1)*X1+1/D+G/D+.5*H/D)/A
      T(6)=(TT1+PP*TT2)*(T(7)+T(8))/(1+PP*(A+1)/A)
      TT3=(.5*(A+1)*X1+1/D+G/D+.5*H/D)
      T(5)=(UU+V/(3*X+1))*((A+1)*T(6)-TT3*(T(7)+T(8)))
      S2=T(5)+T(6)+T(7)+T(8)
      T(8)=100*T(8)/S2
      T(7)=100*T(7)/S2
      T(6)=100*T(6)/S2
      T(5)=100*T(5)/S2
      RETURN
      END
```

Appendix 3.

The program which was used to convert the relative peak heights for the CH_3SO_2, CH_2DSO_2, CHD_2SO_2 and CD_3SO_2 signals (m/e 79 to 82) obtained during the mass spectral analyses of the perdeuterated methanesulfonyl chloride samples generated from the multiexchange reactions to relative quantities is described in this appendix. The program was written in the BASIC computer language. The program has two versions which differ only in the values of the "correction factors" used. These are described in the experimental section of chapter I. The two versions of the program are MS79PL and MS79PH. MS79PL was used to correct the data from the "low" resolution and MS79PH from the "high" resolution mass spectral measurements. A listing of MS79PL appears at the end of this appendix. MS79PH is the same as MS79PL except for the values of the correction factors (C) used.

The program begins by dimensioning the vectors used to contain the twelve correction factors (C), the experimental peak heights (P), the corrected peak heights (D) and the vector (T) used in the calculation of the standard deviations. This is followed by a series of prompts which allows the input of an experiment number, S, the number of times the m/e 79 to 82 region was scanned (a trace), J, and the raw data beginning with the value of the peak heights for m/e 79 for the first trace through to m/e 82 for the last trace as a vector, P. The next section, from line 391 to 720 corrects the raw data for natural abundance. This section prints the corrected raw data and these values normalized to 100% for each trace. Lines 740 to 800 calculate the average results

for all the traces and displays them. The remainder of the program calculates the standard deviation for each average m/e value .



```
00005 REM                    PROGRAM MS79PL
00010 REM     THIS PROGRAM CONVERTS THE RAW MASS SPECTRAL RESULTS
00020 REM  TO THE ISOTOPICALLY CORRECTED RESULTS.
00030 REM     THE VECTOR C CONTAINS THE TWELVE CORRECTION
00040 REM  FACTORS THE VECTOR P CONTAINS THE RAW DATA POINTS FOR
00050 REM  A MAXIMUM OF 7 TRACES. D CONTAINS THE
00060 REM  CORRECTED RESULTS AND T WAS USED IN THE CALCULATION
00070 REM  OF THE STANDARD DEVIATIONS.
00080 DIM C(12),P(30),D(30),T(30)
00090 PRINT "ISOTOPE CORRECTIONS FROM CH3SO2 TO CD3SO2"
00100 REM     THE FOLLOWING PROMPTS ALLOW INPUT OF THE
00110 REM  EXPERIMENT NUMBER,THE NUMBER OF TRACES TAKEN
00120 REM  DURING THE MASS SPECTRAL MEASUREMENT AND THE
00130 REM  RAW DATA POINTS.
00140 REM     THE RAW DATA WAS INPUT BY ASSIGNMENT OF THE
00150 REM  FIRST FOUR ELEMENTS OF P TO CONTAIN THE PEAK
00160 REM  HEIGHTS FOR M/E 79,80,81,82 OF THE FIRST TRACE.
00170 REM  THE SAME VALUES FROM THE SECOND TRACE WERE CONTAINED
00180 REM  IN THE FIFTH TO EIGHTH ELEMENTS OF P. THE REMAINING
00181 REM  TRACES WERE ENTERED IN THE SAME MANNER.
00190 PRINT "FOR MASS SPEC EXPT";
00200 INPUT S
00210 PRINT
00220 PRINT "THE NUMBER OF RUNS WERE";
00230 INPUT J
00240 PRINT "THE RAW DATA POINTS ARE"
00250 MAT INPUT P
00251 REM     THESE WERE THE CORRECTION FACTORS FOR THE LOW
00252 REM  RESOLUTION MEASUREMENTS.
00260 C(1)=.01988
00270 C(2)=.048
00280 C(3)=.00048
00290 C(4)=.01972
00300 C(5)=.048
00310 C(6)=.00048
00320 C(7)=.01956
00330 C(8)=.048
00340 C(9)=.00048
00350 C(10)=.0194
00360 C(11)=.048
00370 C(12)=.00048
00371 REM     THESE TWO STATEMENTS DISPLAY THE CORRECTION FACTORS
00372 REM  USED.
00380 PRINT "THE CORRECTION FACTORS ARE"
00390 MAT PRINT C;
00391 REM     THE NEXT STATEMENT CAUSES THE LOOP TO BE
00392 REM  EXECUTED ONCE FOR EACH TRACE.
00400 FOR I=0 TO J-1
00402 REM     WITH I=0 THE NEXT STATEMENT DIRECTS THE PROGRAM
00403 REM  TO BEGIN BY CORRETING THE PEAK HEIGHT FOR THE FIRST
00404 REM  PEAK OF THE FIRST TRACE.
```

```
00410 K=1+I*4
00411 REM     THE NEXT THREE STATEMENTS CALCULATE THE AMOUNTS
00412 REM  OF THE M/E 79 PEAK THAT APPEAR UNDER THE M/E 80,81
00413 REM  AND 82 PEAKS DUE TO THE NATURAL ABUNDANCES OF THE
00414 REM  ELEMENTS.
00420 F1=C(1)*P(K)
00430 F2=C(2)*P(K)
00440 F3=C(3)*P(K)
00441 REM     THE NEXT STATEMENT GIVES THE CORRECTED PEAK HEIGHT
00442 REM. FOR THE M/E 79 PEAK.
00450 D(K)=P(K)+F1+F2+F3
00451 REM     THE NEXT THREE STATEMENTS REDUCE THE M/E 80,81 AND
00452 REM  82 PEAKS BY THE AMOUNTS OF THE M/E 79 PEAK. THAT APPEARED
00453 REM  UNDER THEM.
00460 D(K+1)=P(K+1)-F1
00470 D(K+2)=P(K+2)-F2
00480 D(K+3)=P(K+3)-F3
00481 REM     THE NEXT SIX STATEMENTS CALCULATE THE CORRECTED
00082 REM  PEAK HEIGHT FOR THE M/E 80 PEAK IN THE SAME MANNER.
00483 REM  NOTE THAT F6 WAS NOT USED TO DIMINISH THE M/E 83 PEAK
00484 REM  SINCE A CORRECTED VALUE FOR THIS PEAK WAS NOT NEEDED.
00490 F4=C(4)*D(K+1)
00500 F5=C(5)*D(K+1)
00510 F6=C(6)*D(K+1)
00520 D(K+1)=D(K+1)+F4+F5+F6
00530 D(K+2)=D(K+2)-F4
00540 D(K+3)=D(K+3)-F5
00541 REM     THE NEXT FIVE STATEMENTS CALCULATE THE CORRECTED PEAK
00542 REM  HEIGHT FOR THE M/E 81 PEAK.NOTE THAT NEW VALUES OF THE M/E
00543 REM  83 AND 84 PEAKS WERE NOT NEEDED AS ABOVE.
00550 F7=C(7)*D(K+2)
00560 F8=C(8)*D(K+2)
00570 F9=C(9)*D(K+2)
00580 D(K+2)=D(K+2)+F7+F8+F9
00590 D(K+3)=D(K+3)-F7
00591 REM     THE NEXT FOUR STATEMENTS CALCULATE THE CORRECTED PEAK
00592 REM  HEIGHT FOR THE M/E 82 PEAK.NOTE THAT NEW VALUES OF TH M/E
00593 REM  83,84 AND 85 PEAKS WERE NOT NEEDED AS ABOVE.
00594 REM
00600 G1=C(10)*D(K+3)
00610 G2=C(11)*D(K+3)
00620 G3=C(12)*D(K+3)
00630 D(K+3)=D(K+3)+G1+G2+G3
00631 REM     THE NEXT NINE STATEMENTS PRINT THE CORRECTED VALUES
00632 REM  FOR EACH TRACE AS WELL AS THE RELATIVE AMOUNTS IN PERCENT.
00640 R=I+1
00650 PRINT "THE RESULTS OF RUN" R "ARE"
00660 PRINT D(K),D(K+1),D(K+2),D(K+3)
00670 S=D(K)+D(K+1)+D(K+2)+D(K+3)
00680 D(K)=100*D(K)/S
00690 D(K+1)=100*D(K+1)/S
```

```
00700 D(K+2)=100*D(K+2)/S
00710 D(K+3)=100*D(K+3)/S
00720 PRINT D(K),D(K+1),D(K+2),D(K+3)
00730 PRINT
00731 REM     THIS STATEMENT SENDS THE PROGRAM TO THE START OF THE LOOP
00732 REM  TO CALCULATE THE CORRECTED PEAK HEIGHTS FOR THE NEXT TRACE.
00740 NEXT I
00741 REM     THE NEXT NINE STATEMENTS AVERAGE THE RESULTS OF ALL J
00742 REM  TRACES.
00750 A1=(D(1)+D(5)+D(9)+D(13)+D(17)+D(21)+D(25))/J
00760 A2=(D(2)+D(6)+D(10)+D(14)+D(18)+D(22)+D(26))/J
00770 A3=(D(3)+D(7)+D(11)+D(15)+D(19)+D(23)+D(27))/J
00780 A4=(D(4)+D(8)+D(12)+D(16)+D(20)+D(24)+D(28))/J
00790 PRINT "THE AVERAGE RESULTS OF THE RUNS ARE"
00800 PRINT A1,A2,A3,A4
00810 PRINT
00821 REM     THE REMAINDER OF THE PROGRAM CALCULATES THE STANDARD
00822 REM  DEVIATIONS FOR THE AVERAGED VALUES USING AN N-1 WEIGHTING.
00820 S1=0.0
00830 S2=0.0
00840 S3=0.0
00850 S4=0.0
00860 FOR I=0 TO J-1
00870 K=1+4*I
00880 T(K)=(D(K)-A1)**2
00890 T(K+1)=(D(K+1)-A2)**2
00900 T(K+2)=(D(K+2)-A3)**2
00910 T(K+3)=(D(K+3)-A4)**2
00920 S1=S1+T(K)
00930 S2=S2+T(K+1)
00940 S3=S3+T(K+2)
00950 S4=S4+T(K+3)
00960 NEXT I
00970 B=J-1
00980 S1=(S1/B)**.5
00990 S2=(S2/B)**.5
01000 S3=(S3/B)**.5
01010 S4=(S4/B)**.5
01020 PRINT "THE STD DEV (N-1) ARE : "
01030 PRINT S1,S2,S3,S4
01040 END
```

Appendix 4

The program used to simulate the reaction of methanesulfonyl chloride with triethylamine and methanol-d in organic solvents according to the reaction mechanism of Figure 2.2 was called SIMTR4. A listing of SIMTR4 is given at the end of this appendix. This program was written in the BASIC computer language.

The first reaction of the program defines the input vectors, intializes these to zero, and accepts the input data through a series of prompts. The first two prompts (statements 109 to 130) allow the user to input the initial "concentrations" of sulfonyl chloride, base and methanol-d (C, N, M(2)).

The next three prompts (statements 140 to 190) allow the user to define which mechanistic variation (see chapter 2) would be simulated by the program by assigning values of 1 or 0 to x, y, and z in the following manner. For variation:

A. Set x = 0 to precipitate the base hydrochloride before it can participate in any other process
   Set y = 0 or 1
   Set z = 0 or 1

B. Set x = 1 to keep the base hydrochloride in solution. Set y = 0 to exchange the hydrogen of the base hydrochloride generated during sulfene formation before the sulfene is trapped. Set z = 1 to keep the base hydrochloride in solution.

C. Set x = 1

Set y = 0

Set z = 0 to precipitate the base hydrochloride after hydrogen-deuterium exchange has occurred.

D. Set x = 1

Set y = 1 to delay exchange of the hydrogen of the base hydrochloride generated during sulfene formation until the sulfene is trapped. Set z = 1.

E. Set x = 1

Set y = 1

Set z = 0

The next three prompts (statements 200 to 260) control the simulation time and the display of the output. Tl is the time interval (or Δt) and H is the total reaction time. These are both arbitrary units. H was normally set to 10 and Tl to 0.001. H and Tl were used to calculate G which is the integer value of H/Tl and represents the number of time steps that the reaction was simulated over. P is used to specify the points during the simulation that the concentrations are printed. As an example, if H = 10, Tl = 0.001 and P was set at 2000 then the concentrations would be printed at 20, 40, 60, 80 and 100% of the total reaction time.

The final prompt (statements 270 and 280) allow the user to input the relative rate constants as defined in Figure 2.2.

The next section of SIMTR4, statements 310 to 810, performs the simulation calculating the change in concentrations in the time

interval (Tl) and adding these changes to the previous concentrations. This is repeated 6 times. If the concentration of any species falls below 1×10^{-10} its concentration was set to zero.

Statements 830 and 1020 comprise the subroutine which averages the active hydrogen and deuterium over the available sites. These were the base hydrochloride (B(1)), base deuterochloride (B(2)), methanol (M(1)) and methanol-d (M(2)).

```
00005 REM                    PROGRAM SIMTR4
00010 REM      PROGRAM TO SIMULATE THE REACTION OF CH3SO2NET2ME FSO3
00020 REM  WITH ET3N IN ORGANIC SOLVENTS.
00030 DIM M(10),B(10),E(10),K(10)
00040 FOR I=1 TO 10
00050 M(I)=0.0
00060 E(I)=0.0
00070 B(I)=0.0
00080 K(I)=0.0
00090 NEXT I
00101 REM     THE FOLLOWING SERIES OF PROMPTS WERE USED TO SPECIFY;
00102 REM  THE INITIAL CONCENTRATIONS,THE X,Y,OR Z USED TO STIPULATE
00104 REM  THE ASSUMED TIMING OF THE PRECIPITATION OF THE BASE HYDRO-
00105 REM  AND DEUTEROCHLORIDES (IF X,Y OR Z WERE NOT SET TO ZERO THEY
00106 REM  WERE SET TO ONE),THE TIME INTERVAL,THE TOTAL SIMULATION TIME,
00107 REM  WHEN TO PRINT INTERIM RESULTS,AND THE RATE CONSTANTS K(1) TO
00108 REM  K(4).
00109 PRINT "THE INITIAL CONC OF SULFONYL CHLORIDE IS"
00110 INPUT C
00120 PRINT "THE CONCS OF BASE AND MEOD ARE"
00130 INPUT N,M(2)
00140 PRINT "IF PRCP FAST INPUT X=0"
00150 INPUT X
00160 PRINT "IF EQUIL OF HYDROGEN BEFORE SULFENE TRAPPING INPUT Y=0"
00170 INPUT Y
00180 PRINT "IF PRCP COMPLETE IN EACH TIME STEP INPUT Z=0"
00190 INPUT Z
00200 PRINT "TIME INTERVAL IS"
00210 INPUT T1
00220 PRINT "TOTAL SIMULATION TIME IS"
00230 INPUT H
00240 G=INT(H/T1)
00250 PRINT "THE RESULTS AFTER HOW MANY TIME STEPS"
00260 INPUT P
00270 PRINT "THE RATE CONSTANTS ARE"
00280 MAT INPUT K
00290 PRINT
00291 REM     THE NEXT STATEMENT INITIALIZES THE TOTAL REACTION
00292 REM  TIME T TO ZERO
00300 T=0
00301 REM     STATEMENT 310 DIRECTS THE PROGRAM TO PERFORM THE DO LOOP
00302 REM  WHICH CALCULATES THE CHANGE IN CONCENTRATION FOR EACH
00303 REM  SPECIES OVER THE TIME INTERVAL T1 AND THE NEW CONCENTRATIONS
00304 REM  WHICH RESULT.THIS LOOP WAS REPEATED G TIMES IN ORDER TO
00305 REM  SIMULATE THE FINAL CONCENTRATIONS OF REACTANTS AND PRODUCTS.
00306 REM     THE LOOP ALSO CONTAINS A SERIES OF IF STATEMENTS TO
00307 REM  ASSIGN A CONCENTRATION OF ZERO TO ANY SPECIES WHOSE
00308 REM  CONCENTRATION FELL BELOW 1.0E-10.
00310 FOR I= 0 TO G
00311 REM     STATEMENT 320 DIRECTS THE PROGRAM TO PRINT THE INITIAL
00312 REM  CONCENTRATIONS.
00320 IF T=0 THEN 730
00330 IF C>1E-10 THEN  350
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00340 C=0.0
00350 IF N>1E-10 THEN 370
00360 N=0.0
00370 C1=-K(1)*N*C
00380 IF X=0.0 THEN 410
00390 B1=K(1)*N*C
00400 GO TO 420
00410 B1=0
00420 N1=-K(1)*N*C-K(4)*E(1)*N-K(4)*E(2)*N
00430 IF E(1)>1E-10 THEN 450
00440 E(1)=0.0
00450 IF E(2)>1E-10 THEN 470
00460 E(2)=0.0
00461 REM     IF STATEMENT 470 DIRECTS THE PROGRAM TO AVOID THE
00462 REM  SUBROUTINE WHICH EQUILIBRATES THE HYDROGEN AND DEUTERIUM
00463 REM  OVER THE POSSIBLE SITES IF THE ASSUMPTION THAT THE EQUILIBRA-
00465 REM  TION OF HYDROGEN OCCURED AFTER SULFENE TRAPPING (IE. Y=1).
00470 IF Y=1 THEN 490
00480 GOSUB 830
00481 REM     THE NEXT SECTION, LINES 490 TO 680,CALCULATES THE
00482 REM  CONCENTRATIONS WHICH WOULD BE PRESENT AT THE END OF THE
00483 REM  CURRENT TIME INTERVAL.
00490 IF M(2)>1E-10 THEN 510
00500 M(2)=0.0
00510 IF M(1)>1E-10 THEN 530
00520 M(1)=0.0
00530 IF S>1E-10 THEN 550
00540 S=0.0
00550 S1=K(1)*N*C-K(2)*S*M(2)-K(3)*S*M(1)
00560 E1=K(3)*S*M(1)-K(4)*E(1)*N
00570 E2=K(2)*S*M(2)-K(4)*E(2)*N
00580 R1=K(4)*E(1)*N+K(4)*E(2)*N
00590 M2=-K(2)*S*M(2)
00600 M1=-K(3)*S*M(1)
00610 C=C+C1*T1
00620 N=N+N1*T1
00630 S=S+S1*T1
00640 E(1)=E(1)+E1*T1
00650 E(2)=E(2)+E2*T1
00660 R=R+R1*T1
00670 M(2)=M(2)+M2*T1
00680 M(1)=M(1)+M1*T1
00681 REM     THIS IF STATEMENT DIRECTS THE PROGRAM TO BYPASS THE
00682 REM  SUBROUTINE SINCE, IF Y=0 THE SUBROUTINE WOULD HAVE BEEN
00683 REM  CALLED AT STATEMENT 480.
00690 IF Y=0.0 GO TO 710
00700 GOSUB 830
00701 REM     THIS IF STATEMENT DIRECTS THE PROGRAM TO PRINT THE
00702 REM  CONCENTRATIONS IF THE INTEGER VALUE OF THE LOOP COUNTER
00703 REM  I/P WAS EQUAL TO I/P. THIS ALLOWS THE PROGRAM TO DISPLAY
00704 REM  THE CONCENTRATIONS AT INTERMEDIATE STAGES OF THE SIMULATION.
00710 IF INT(I/P)=I/P THEN 730
00720 GO TO 800
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00730 PRINT "SULFONYL CHLORIDE CONC IS" C
00740 PRINT "BASE CONC IS "N
00750 PRINT "SULFENE CONC IS" S
00760 PRINT "AMOUNT ESTERS ARE" E(1),E(2)
00770 PRINT "AMOUNT RESIDUE IS" R
00780 PRINT "ALCOHOL CONCS ARE" M(1),M(2)
00790 PRINT
00800 T=T+T1
00801 REM     STATEMENT 800 INCREMENTS THE TOTAL SIMULATION TIME BY T1
00802 REM  AND 810 DIRECTS THE PROGRAM TO THE START OF THE LOOP SO THAT
00803 REM  THE NEXT TIME SEGMENT OF THE REACTION COULD BE SIMULATED.
00810 NEXT I
00820 GO TO 1030
00821 REM     STATEMENT 830 INCREASES THE BASE HYDROCHLORIDE CONCENTRA-
00822 REM  TION AS IF THERE WAS NO PRECIPITATION UNTIL ALL THE GENERATED
00823 REM  SULFENE WAS CONSUMED.
00830 B(1)=B(1)+B1*T1
00831 REM     STATEMENTS 840 TO 870 RESET THE AMMONIUM ION
00832 REM  CONCENTRATIONS TO ZERO FOR THE CASE WHERE PRECIPITATION
00833 REM  WAS FAST AND DIRECT THE PROGRAM TO STATEMENT 910 WHICH
00834 REM  BEGINS THE CALCULATION OF THE EQUILIBRATED CONCENTRATIONS
00835 REM  OF THE BASE HYDROCHLORIDE, BASE DEUTEROCHLORIDE, METHANOL
00836 REM  AND METHANOL-O-D.
00840 IF X=1 THEN 880
00850 B(1)=0.0
00860 B(2)=0.0
00870 GO TO 910
00871 REM     THE NEXT SECTION RESETS THE BASE HYDRO- AND DEUTERO-
00872 REM  CHLORIDE CONCENTRATIONS FOR THE CASE WHERE PRECIP-
00873 REM  ITATION WAS SLOW BUT COMPLETE AFTER EACH TIME STEP.
00880 IF Z=1 THEN 910
00890 B(1)=B1*T1
00900 B(2)=0.0
00903 REM     THE REMAINDER OF THE PROGRAM EQUILIBRATES THE
00904 REM  HYDROGENS AND DEUTERIUMS OVER THE AVAILABLE SITES AND
00905 REM  RESETS THE BASE HYDRO- AND DEUTEROCHLORIDE CONCENTRATIONS
00906 REM  TO ZERO IF PRCP COMPLETE AFTER THE TIME STEP (IE. Z=0).
00910 D=M(2)
00920 E=B(2)
00930 J=M(1)
00940 L=B(1)
00950 M(2)=(D+E)*(D+J)/(D+J+L+E)
00960 M(1)=(J+L)*(D+J)/(D+J+L+E)
00970 B(2)=(L+E)*(D+E)/(D+J+L+E)
00980 B(1)=(L+E)*(J+L)/(D+J+L+E)
00990 IF Z=1 THEN 1020
01000 B(1)=0.0
01010 B(2)=0.0
01020 RETURN
01030 END
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END

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FIN